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NOVEMBER, 15, 1922

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

AUGUST, 1922. NUMBER 2

Absorption of Digitalis in Man. Cary Eggleston, M.D., and John Wyckoff, M.D., New York.

Delayed Conduction Through the Right and Left Branches of the Atrioventricular Bundle. Horace Marshall Kerns, M.D., Cleveland.

Studies on the Physiology of the Liver. III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver. Frank C. Mann, M.D., and Thomas Byrd Magath, M.D., Rochester, Minn.

The Mechanism of Hay-Fever. Francis M. Rackemann, M.D., Boston.

Studies of Cerebrospinal Fluid and Blood of Syphilitic and Normal Persons, with Special Reference to the Immunity Reactions and the Colloidal Gold Test on the Original and Ultrafiltered Fluids and Serums. Charles E. Nixon, M.D., and Koichi Naito, M.D., Minneapolis.

An Efficient and Practical Method for the Counting of Red Blood Cells. Theo. R. Waugh, M.D., Montreal.

Factors in Leukocytosis. Donald K. Bacon, M.D., St. Paul, Minn.; Frank O. Novy, M.D., and Hazel H. Eppler, Detroit.

Blood Pressure and Pulse Rate Reactions. Second Paper. T. Addis, M.D., San Francisco.

SEPTEMBER, 1922. NUMBER 3

Interpretations of the Initial Phases of the Electrocardiogram with Special Reference to the Theory of "Limited Potential Differences." Sir Thomas Lewis, M.D., F.R.C.P., London.

A Case of Hodgkin's Disease Treated with Roentgen Rays for Six Years. Kenneth R. McAlpin, M.D., and William C. Von Glahn, M.D., New York.

Experimental Reproduction of the Specific Histopathology of Influenza. George Baehr, M.D., and Leo Loewe, M.D., New York.

The Mechanism of the Development of Nonbacterial, Chronic Cardiovalvular Disease. William Thalhimer, M.D., Milwaukee.

Bronchospirochetosis in China. Ernest Carroll Faust, Ph.D., Peking, China.

Tetany. A Report of Cases with Acid-Base Disturbance. Samuel B. Grant, M.D., Boston.

The Blood Pressure of Normal Cantonese Students. Wm. W. Cadbury, M.D., Canton, China.

Renal Function and the Amount of Functioning Tissue. T. Addis, M.D., San Francisco.

Studies in the Kottmann Reaction for Thyroid Activity. W. F. Petersen, M.D.; F. T. H'Doubler, M.D., and J. E. F. Laibe, M.D., Chicago.

The Glucose Mobilization Rate in Hyperthyroidism. Bertram J. Sanger, M.D., and Elsie G. Hun, New York.

Book Reviews.

OCTOBER, 1922. NUMBER 4

Studies on the Visceral Sensory Nervous System. XIV. The Reflex Control of the Cardia and Lower Esophagus in Mammals. A. J. Carlson, Ph.D., M.D.; T. E. Boyd, and J. F. Pearcy, Chicago.

Electrocardiography and Prognosis. I. Significant T Wave Negativity in Isolated and Combined Derivations of the Electrocardiogram. Frederick A. Willius, Rochester, Minn.

Clinical Studies of Quinidin. II. Alterations in the Cardiac Mechanism After Administration of Quinidin to Patients with Auricular Fibrillation with Consideration of Certain Toxic Effects of the Drug. Robert L. Levy, M.D., New York.

A Study of the Erythrocyte Curve at Various Ages and Its Relationship to Hemoglobin Curve. Laurence Hampson Mayers, A.M., M.D., Chicago.

Intravitam Bone Marrow Studies. Preliminary Report. Part I. Description of a Marrow Trephine and Experimental Studies. Laird M. Morris, M.D., and Ernest H. Falconer, M.D., San Francisco.

Intravitam Bone Marrow Studies. Part II. Survey of the Clinical Field. Laird M. Morris, M.D., and Ernest H. Falconer, M.D., San Francisco.

The Basal Metabolism in Nontoxic Goiter and in Borderline Thyroid Cases, with Particular Reference to Its Bearing in Differential Diagnosis. James H. Means, M.D., and Harriet W. Burgess, A.B., Boston.

The Alkalimetry of Whole Blood. Second Paper: The Acid Fixing of the Blood in Renal Disease. John B. Rieger, M.D., and Hugo A. Freund, M.D., Detroit.

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Archives of Internal Medicine

VOL. 30 NOVEMBER, 1922 No. 5

INTERPRETATION OF THE WASSERMANN REACTION

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KANSAS CITY, MO.

One hesitates in the present day to write on a subject which has been so ably and fully discussed as the Wassermann reaction,[1] and to add to a literature already large. During a clinical experience of about seven years, however, in which Wassermann tests have been made as a routine measure in our medical examinations, we have had an unusual opportunity of seeing the value of the test in clinical medicine, and since our tests have been made with both sensitive and coarse (or insensitive) methods simultaneously, we have also had an opportunity to observe the value and dependability of several technics. We wish, therefore, to present briefly data and conclusions gained from more than 50,000 tests on more than 10,000 specimens of blood taken from patients the majority of whom we examined ourselves. Our Wassermann technic has been changed in some of its details from time to time. For this reason, some of the tabulations reported are based on only fifteen hundred consecutive medical cases in which the exact methods to be described have been used. All of the patients from whom this data was obtained were examined carefully, and in our examinations we endeavored to disclose and record every abnormality which could be brought to light by history, physical examination, special examinations, clinical pathology and roentgenology.

I may say at the outset that this paper presents nothing new to the careful serologist nor internist. It is rather a compilation of statistics for the purpose of comparing clinical and serologic findings. It is written partly with a hope of helping restore confidence in the Wassermann reaction in the minds of physicians who may have lost respect for the test on account of contradictory reports given them by serologists who have used widely differing methods.

1. It hardly comes within the scope of this paper to cite the many brilliant researches which have led to our present knowledge of serology in its relationship to the diagnosis and treatment of syphilis. For a review of this literature the reader is referred to the monographs of Noguchi, Craig, Kolmer, etc.

DEVELOPMENT OF THE WASSERMANN TECHNIC

In the early days of Wassermann work, opinions were in harmony concerning the significance of a positive reaction and the relative frequency with which positive reactions were obtained in the different stages of syphilis. It was conceded by the majority of observers that a four plus reaction was given by few, if any, diseases other than syphilis; that a negative reaction did not exclude a diagnosis of syphilis; that the vast majority of secondary cases gave positive reactions, but that a smaller proportion of the primary, tertiary and so-called latent cases gave positive reactions.

The technic as originally used was relatively crude and insensitive. The disease had to be moderately active in order to give a positive reaction. For this reason the Wassermann test failed where it was most needed—that is, in disclosing the disease in late cases in which the symptoms were not well defined.

A number of unique methods were devised for making the test more sensitive, thereby making it possible to obtain a larger proportion of positive reactions in the less active cases. The more important of the measures were the use of reenforced antigens, the use of one unit of complement instead of two units, and finally, incubation at icebox temperature in place of incubation at a temperature of 38 C. These modifications made it possible to carry out a Wassermann reaction which was far more delicate than tests carried out by the method as originally described. The great advantage derived from the modifications was a test which would give positive reactions in the vast majority of cases of syphilis whether early or late. It was offset by a serious disadvantage—namely, unreliability. With the modified method, positive reactions were obtained in a certain proportion of patients who did not have demonstrable syphilis.

At the present time one or all of the modifications mentioned are used in some laboratories, while in others the test used is not materially different from the original Wassermann test. The result is that in some laboratories a method is used which is much more sensitive than that used in other laboratories. Unfortunately, results are reported by the majority of laboratories in the same symbols as those used early in Wassermann work—namely, negative, one plus, two plus, three plus and four plus, regardless of whether the test used is comparatively insensitive, as was the original Wassermann test, or exceedingly sensitive. As a result, practitioners at the present time may send blood to several laboratories and receive a different report from each.

Disagreements of this sort have caused a plea from all quarters for a standard test which might make it possible for all laboratories to obtain uniform results. Such disagreements have also induced a prevalent

belief among physicians in many localities that the Wassermann test is almost worthless, that it is merely a symptom of disease, and an unreliable one at that. What is to blame for this situation?

In my opinion it is not due so much to the use of the unique improvements in technic which have made the test more sensitive, nor to the lack of a standard test, as to the fact that all Wassermann reactions, whether obtained by sensitive or insensitive methods, are reported in the same technical and inadequate terms—one plus, two plus, three plus and four plus. Some of the discrepancies would be avoided if the reports were made in plain English words which would have the same meaning to all serologists and to all physicians, such, for example, as doubtful, weakly positive and strongly positive. A result labeled strongly positive would surely never be reported or accepted on the basis of a four plus reaction obtained by the more sensitive methods.

The ideal Wassermann reaction, unfortunately, can never be realized through the use of any one single test, no matter what technic is used. An ideal Wassermann test would be one sensitive enough to come out

TABLE 1.—DESCRIPTION OF TESTS 1 TO 5

	Test 1	Test 2	Test 3	Test 4	Test 5
Antigen	Cholesterinized 0.4%	Cholesterinized 0.2%	Cholesterinized 0.2%	Acetone insoluble	Alcoholic extract
Complement	1 unit	1 unit	2 units	2 units	2 units
Sensitiveness of test	Extremely sensitive	Very sensitive	Moderately sensitive	Moderately sensitive	Moderately sensitive

positive in every case of syphilis, whether early or late, and, at the same time, so insensitive as to never give a false positive. Such a test is theoretically and practically impossible. A test sensitive enough to come out positive almost invariably in patients with late syphilis is, of necessity, so sensitive that it will come out positive in a certain proportion of patients not afflicted with syphilis. As a practical alternative, I have used a five tube test. Two of the tubes are sensitive enough to give a positive result in the great majority of patients with syphilis, whether early or late, two tubes are so coarse, or insensitive, as virtually never to give a false positive result, and one tube is intermediate.

METHOD

My plan for setting up Wassermann tests may be criticized as being unnecessarily complex. At the same time, it has given me an unusual opportunity of observing the clinical significance of several types of technic.

Briefly the method is as follows: Tube 1 contains cholesterinized antigen (0.4 per cent.) with one unit of complement. Tube 2 contains

cholesterinized antigen (0.2 per cent.) with one unit of complement. Tube 3 contains cholesterinized antigen (0.2 per cent.) with two units of complement. Tube 4 contains acetone insoluble antigen (noncholesterinized) with two units of complement. Tube 5 contains alcoholic extract (noncholesterinized) with two units of complement.

From one-fourth to one-fifth of a slightly anticomplementary quantity of antigen was used in tube 1 and from one-fifth to one-eighth (this has been changed from time to time) in tubes 2, 3, 4 and 5; 0.05 c.c. of inactivated patient's serum was used in all tubes; total volume of tests 1.25 c.c.; incubation icewater bath at 8 C. one hour; sheep system.[2]

While this method is rather complex it presents one real advantage, namely, its scope. It includes two tests which are exceedingly sensitive, two tests which are moderately coarse, and one intermediate test.

THE COMPARATIVE DELICACY OF DIFFERENT WASSERMANN METHODS

The comparative delicacy of the five tests described is shown in Tables 2 and 3. In these two tables, however, two tubes were added to the five ordinarily used. The technic used in these two additional tests (Tests 6 and 7) was the same, respectively, as that used in Tubes 4 and 5, except that they were incubated at 38 C. instead of 8 C., as were tubes 1, 2, 3, 4 and 5. Two known positive specific bloods were titrated down with the technic of each test (Tests 1 to 7) starting with 0.1 c.c. of blood serum and ending with $\frac{1}{4000}$ c.c. By noting the smallest quantity of serum required to give a four plus reaction in each tube one can observe the relative delicacy of each of the seven methods.

Test 7 (Table 2) gave a four plus reaction with $\frac{1}{80}$ c.c. of blood, while approximately one-half this amount, or $\frac{1}{160}$ c.c., was sufficient to give a four plus reaction in tests 4 and 5 (same tests as 5 and 7, except for the use of icewater bath incubation); approximately one-fourth that amount, or $\frac{1}{320}$ c.c., was sufficient to give a four plus reaction in test 3 (same test as 4 and 5, except for the use of cholesterinized antigen); approximately one-eighth this amount, or $\frac{1}{640}$ c.c., was sufficient to give a four plus reaction in test 2 (same as test 3, except for the use of one unit of complement instead of two units); and approximately one-sixteenth this amount, or $\frac{1}{1280}$ c.c., was sufficient to give a four plus reaction with test 1 (same as test 2, except that more antigen and more cholesterin was used). In other words, the technic used in test 1 was approximately sixteen times as sensitive as that of tests 6 and 7, which have relatively the same delicacy

2. Duke, W. W.: Ice Water Bath in Complement Fixation for the Wassermann Reaction. A Shortened Technic, Am. J. Syph. 5:312 (April) 1921.

TABLE 2.—TITRATIONS OF A STRONG POSITIVE BLOOD BY SEVEN DIFFERENT TECHNICS TO SHOW THEIR COMPARATIVE DELICACY

	Technic 1	Technic 2	Technic 3	Technic 4	Technic 5	Technic 6	Technic 7
Antigen	0.4% C.	0.2% C.	0.2% C.	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized
Complement	1 U	1 U	2 U	2 U	2 U	2 U	2 U
Temp. of fixation	8 C.	8 C.	8 C.	8 C.	8 C.	37.5 C.	37.5 C.
Serum, C.c.							
1:10	4+	4+	4+	4+	4+	4+	4+
1:15	4+	4+	4+	4+	4+	4+	4+
1:20	4+	4+	4+	4+	4+	4+	4+
1:30	4+	4+	4+	4+	4+	4+	4+
1:40	4+	4+	4+	4+	4+	4+	4−
1:60	4+	4+	4+	4+	4+	4+	4−
1:80	4+	4+	4+	4+	4+	4+	4−
1:120	4+	4+	4+	4+	4+	3+	3−
1:160	4+	4+	4+	4+	4+	2+	—
1:240	4+	4+	4+	2+	2+	—	—
1:320	4+	4+	4+	—	—	—	—
1:480	4+	4+	1+	—	—	—	—
1:640	4+	4+	—	—	—	—	—
1:960	4+	3+	—	—	—	—	—
1:1280	4+	2+	—	—	—	—	—
1:1440	2+	1+	—	—	—	—	—
1:1600	1+	—	—	—	—	—	—

TABLE 3.—TITRATIONS OF A STRONG POSITIVE BLOOD BY SEVEN DIFFERENT TECHNICS TO SHOW THEIR COMPARATIVE DELICACY. TECHNICS DESCRIBED BELOW

	Technic 1	Technic 2	Technic 3	Technic 4	Technic 5	Technic 6	Technic 7
Antigen	0.4% C.	0.2% C.	0.2% C.	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized	Non-cholesterinized
Complement	1 U	1 U	2 U	2 U	2 U	2 U	2 U
Temp. of fixation	8 C.	8 C.	8 C.	8 C.	8 C.	37.5 C.	37.5 C.
Serum, C.c.							
1:10	4+	4+	4+	4+	4+	4+	3−
1:15	4+	4+	4+	4+	4+	3+	2+
1:20	4+	4+	4+	4+	4+	1+	1+
1:30	4+	4+	4+	4+	4+	—	—
1:40	4+	4+	4+	4+	4+	—	—
1:60	4+	4+	4+	4+	4+	—	—
1:80	4+	4+	4+	4+	4+	—	—
1:120	4+	4+	4+	3+	3+	—	—
1:160	4+	4+	4+	—	—	—	—
1:240	4+	4+	1+	—	—	—	—
1:320	4+	3+	—	—	—	—	—
1:480	4+	1+	—	—	—	—	—
1:640	2+	—	—	—	—	—	—
1:960	1+	—	—	—	—	—	—
1:1280	—	—	—	—	—	—	—
1:1440	—	—	—	—	—	—	—
1:1600	—	—	—	—	—	—	—

as the original Wassermann. A number of similar titrations with different specimens of blood have shown essentially the same result. With other bloods, however, a much greater difference was frequently encountered between tests 4 and 5, on the one hand, and tests 6 and 7 on the other (where warm water bath fixation was used). Table 3, for example, shows that tests 4 and 5 were about eight times as sensitive as were tests 6 and 7.

One might point out another factor of interest which can be observed in these tables, namely, the relatively small difference in the amounts of serum required to give a four plus and a one plus reaction by each test. Regardless of technic, a four plus reaction was given by little or no more than twice the amount of serum required to give a one plus reaction. The difference, then, between a one plus reaction and a four plus reaction is not great, in fact, a one plus reaction by technics 4, 5, 6 and 7 has much more real significance than a four plus reaction given by technics 1 or 2.

It may be repeated here, that in some laboratories a four plus reaction is reported on the basis of a result obtained by a test as delicate as my tube 1, while in other laboratories a four plus reaction is reported only on the basis of a four plus reaction obtained by a test relatively as coarse as that described for tubes 4 and 5, or, in some laboratories, even as coarse as tubes 6 and 7. So long as this is the case, and results are reported regardless of technic in the same technical terms—one, two, three and four plus, opinions will differ concerning the reactions given by doubtful and weakly positive bloods.

STATISTICS

My statistics are based on a study of patients referred to me for general medical examination. So few were referred because of primary or secondary syphilis that this type of case can virtually be excluded from the tabulations. The statistics are based on a study of miscellaneous chronic medical cases, in 10.7 per cent. of which active syphilis was demonstrable and a very large per cent. of these showed involvement of the central nervous system.

To give the Wassermann reaction its proper place in a clinical diagnosis one must know the actual value and significance of a positive reaction and of a negative reaction for the method used. This varies greatly with different methods. Unless one realizes this fact, and understands exactly what his positive and his negative reactions indicate, the Wassermann reaction may be very misleading, as is shown by the data obtained with the different tests as reported in Tables 4 and 5.

Test 1 gave a four plus reaction in 95 per cent. of patients in whom syphilis was found clinically. It was from one to three plus in 4 per

cent. of the remaining 5 per cent., and negative in less than 1 per cent. In fact, we have on our records only two patients who had syphilis positively proven (and who were not recently treated) who gave a flat negative reaction with test 1. These two patients had very active syphilis, both recovered under treatment but gave persistently negative Wassermann reactions with both blood and spinal fluid. Test 1 gave a four plus reaction in 31.5 per cent. of consecutive medical cases with miscellaneous diseases (including syphilis), and in these cases syphilis was found clinically in only 32.2 per cent. The four plus reactions given by this technic were, therefore, false positives in 67.8 per cent. of cases. It is quite evident, therefore, that while a negative reaction with test 1 is of great value in the exclusion of syphilis (error

TABLE 4.—PERCENTAGE OF POSITIVE REACTIONS GIVEN BY TESTS 1 TO 5 IN MISCELLANEOUS MEDICAL CASES (INCLUDING SYPHILIS) AND IN PATIENTS WITH SYPHILIS; ALSO THE APPARENT PERCENTAGE OF FALSE POSITIVES

	Test 1	Test 2	Test 3	Test 4	Test 5
4+ reactions in miscellaneous medical cases	31.5%	13.2%	8.5%	6.2%	5.8%
4+ reactions in patients with syphilis	95 %	84 %	75 %	59 %	57 %
Percentage of false positives given by tests	67.8%	34 %	7.3%	Less than 2% (?)	Less than 2% (?)

TABLE 5.—PERCENTAGE OF FALSE POSITIVES GIVEN BY THE FOUR TYPES OF REACTION SHOWN BELOW. THESE PERCENTAGES DIFFER FROM THOSE OF TABLE 4, LINE 3, BUT ARE BELIEVED TO PICTURE MORE CORRECTLY THE ACTUAL VALUE OF THE POSITIVE REACTIONS FOR EACH TEST

Test 1	Test 2	Test 3	Test 4	Test 5	False Positives
4+	—	—	—	—	93.5%
4+	4+	—	—	—	79%
4+	4+	4+	—	—	30%
4+	4+	4+	4+	4+	Less than 2%

very small), a positive reaction is of no value whatever in its positive diagnosis.

At this point, I wish to call attention to a very misleading fact. I stated that more than 67 per cent. of the four plus reactions obtained with test 1 were apparently false positives. While this is true, the impression conveyed is incorrect. To know the dependability of a four plus reaction with a given test (for example, test 1) one must not tabulate all cases which give a four plus reaction with that test (including both strongly positive and mildly positive bloods) but must take only such bloods as give a four plus reaction by this technic alone—that is, bloods which are too mildly positive to give a four plus reaction with the less sensitive tests. To repeat for the sake of clear-

ness, it is necessary, in order to determine the actual value of a positive reaction with a given technic (such as that of test 1) to exclude from the tabulations bloods which give strong positive reactions (such as 4+ 4+ 4+ 4+ 4+ or 4+ 4+ 4+ ——, etc., by the five tube test). Conclusions must be drawn only from bloods which give 4+ ——— reactions. We have compared bloods which gave this latter type of reaction (namely 4+ ———) with clinical findings in a large series of cases, and, surprising to relate, only 6.5 per cent. of the patients had syphilis which could be demonstrated by other means; in other words, actually 93.5 per cent. of the positives of this type were apparently false positives. We believe, therefore, that a test so sensitive as that obtained by the use of a 0.4 per cent. cholesterinized antigen, with one unit of complement and icewater bath incubation, is absolutely worthless so far as the positive diagnosis of syphilis is concerned. A negative reaction, however, is very useful in the exclusion of syphilis.

The results obtained with test 2 were much the same as those obtained with test 1. This test came out four plus in 84 per cent. of patients who had positively proven syphilis, and in 13.2 per cent. of medical patients with miscellaneous diseases (including syphilis). Of this 13.2 per cent., syphilis was found in only 66 per cent. The four plus reactions given by test 2, therefore, were false positives in 34 per cent. of cases. This latter figure also gives an erroneous idea concerning the reliability of a positive reaction with technic 2. As previously stated, the reliability of a test must not be based on a tabulation of all bloods which give a positive reaction with that test but only those which are sufficiently positive to give a positive reaction with that test; in other words, on bloods which give positive reactions with tests 1 and 2 with negative reactions with tests 3, 4 and 5. In bloods of this type (i. e. 4+ 4+ ———) syphilis was demonstrated in only 21 per cent.—that is, of the positives of this class 79 per cent. were apparently false positives. Test 2, therefore, in which 0.2 per cent. cholesterinized antigen was used with one unit of complement and icewater bath incubation, would appear to be worthless in the positive diagnosis of syphilis. A negative reaction with this test is of less value in the exclusion of syphilis than with test 1.

The most interesting and also the most misleading statistical facts were obtained through tabulations of test 3. Test 3 came out four plus in 75 per cent. of patients who had proven syphilis. It came out four plus in 8.5 per cent. of miscellaneous medical cases (including syphilis). Of these positives syphilis was found in 92.7 per cent. Only 7.3 per cent. of positives with test 3, therefore, were false positives. The reliability of positives with test 3, however, cannot be based on these statistics. While the facts are correct, the impression given by them is most erroneous. Of the patients who gave four plus

reactions with tests 1, 2 and 3, with negative reactions with tests 4 and 5 (that is 4 + 4 + 4 + — —) syphilis was demonstrated in only 70 per cent.; in other words, of the bloods barely strong enough to give a positive four plus with tests 1, 2 and 3 (that is 4 + 4 + 4 + — —), 30 per cent. were false positives. We believe, therefore, that test 3, carried out with cholesterinized antigen (0.2 per cent.), two units of complement, and icewater bath fixation, is of no value as a diagnostic test. It appears from the data at hand to be the borderline test which is to sensitive to give reliable positives and too coarse to give dependable negatives.

Tests 4 and 5 came out four plus in only 59 and 57 per cent., respectively, of patients having demonstrable syphilis. They came out negative to three plus in 41 and 43 per cent., respectively, of persons in whom syphilis was demonstrated clinically. In marked contrast with the previous tests, they gave no definitely proven false positives so far as I have been able to determine. I demonstrated the presence of active syphilis through history, physical examination, lumbar puncture, or therapeutic test in 98 per cent. of patients who gave this type of reaction (namely 4 + 4 + 4 + 4 + 4 +). In the remaining 2 per cent., syphilis was not proven. I must add, however, that this 2 per cent. of cases were not adequately examined on account of insufficient time or lack of cooperation on the part of the patient. Tests 4 and 5 in which noncholesterinized antigens were used with two units of complement and icewater bath incubation, appeared to be the most sensitive technics which could be used if reliable positives were to be obtained. In fact, if I were to alter my technic at the present time, I would, for the sake of dependability, make tests 4 and 5 a little less sensitive. I must admit also that while I stated that four plus reactions in tubes 4 and 5 were almost proof positive of syphilis the actual dependability of these two tests could be more accurately estimated by examination of a group of patients who gave four plus reactions in these two tubes with negatives in tests a little less sensitive. Unfortunately I have no statistics of this sort to tabulate.

FALSE POSITIVE REACTIONS WITH TESTS 1, 2 AND 3

As stated previously, tests 1, 2 and 3 give a surprisingly large number of positive reactions in subjects in whom specific disease could not be demonstrated by other means. In such persons these tests came out positive much more frequently when they were ill and visited a doctor for this reason than when they were tested as candidates to be donors for blood transfusion (apparently healthy persons). It was also observed that false positives of this type were obtained more frequently in patients with goiter (regardless of size and toxicity), extreme ptosis, active tuberculosis, chronic sepsis, hypertension, pernicious anemia, diabetes and atrophic arthritis than in persons who did

not have these diseases. These facts were of only passing interest so that the cases were not tabulated carefully for the purpose of getting accurate statistics. In none of this group of cases which gave false positives with tests 1, 2 and 3, inclusive, but in which syphilis was not demonstrable, were tests 4 and 5 positive.

In Table 6 are recorded twenty-five consecutive cases of tuberculosis (clinically free from syphilis) and twenty-five consecutive cases of late syphilis with the respective Wassermann reactions. It is interesting to contrast the tuberculous cases with their many false positive reactions in the sensitive tubes with the large per cent. of strongly positive reactions given by patients with syphilis.

It is of interest to illustrate by titration (Table 7) the large amount of complement fixing body contained in blood obtained from patients having syphilis as compared with the small amount of complement fixing body contained in the blood of nonsyphilitic goiter cases giving false positives with such sensitive tests as 1 and 2. Table 7 presents a comparison of three bloods (A, B and C) taken from patients with syphilis titrated down with the technic of test 1. For comparison are given titrations by the same method of three bloods taken from goiter patients (X, Y and Z) who were clinically free of syphilis but who gave false positives with tests 1 and 2.

The three bloods taken from patients with syphilis gave four plus reactions even when infinitesmal amounts of serum were used. Blood A, for example, gave a four plus reaction with $\frac{1}{6000}$ c.c. of serum; blood B with $\frac{1}{1500}$ c.c.; blood C with $\frac{1}{750}$ c.c. of serum. In contrast with these, each of three goiter cases (X, Y and Z) gave four plus reactions with $\frac{1}{40}$ c.c. of blood but titrations showed that even as much as $\frac{1}{100}$ c.c. gave negative results. This table illustrates how trifling is the reaction of a false positive blood as compared with the blood of a patient with syphilis. I have frequently examined patients who have been told that their blood gave a four plus reaction and on titrating we found a mild reaction (such as X, Y and Z) and in diagnostic tests found that they gave four plus reactions with test 1 or tests 1 and 2 with negatives in tests 3, 4 and 5. Positive reports based solely on positive findings with sensitive tests may be very misleading.

It can readily be understood after perusal of Table 7 that the four plus reactions of goiter bloods (X, Y and Z) might be four plus one day and flatly negative the next, if only sensitive tests be used. Patients who have so little complement fixing body in their blood as these might easily have just enough to give a positive reaction one day by a sensitive test and none at all the next day. In fact, I have frequently encountered bloods of this sort. One could judge, however, from these titrations (A, B and C) how difficult it would be for a real case of syphilis having actually a strongly positive test to give a positive reaction

TABLE 6.—WASSERMANN REACTIONS GIVEN BY TWENTY-FIVE CONSECUTIVE CASES EACH OF TUBERCULOSIS AND SYPHILIS

No.	Syphilis					Tuberculosis				
	Test 1	Test 2	Test 3	Test 4	Test 5	Test 1	Test 2	Test 3	Test 4	Test 5
1	4+	4+	4+	4+	4+	3+	—	—	—	—
2	4+	4+	4+	3+	1+	—	—	—	—	—
3	4+	4+	4+	4+	4+	1+	—	—	—	—
4	4+	4+	4+	—	—	4+	4+	—	—	—
5	4+	4+	4+	4+	4+	4+	3+	—	—	—
6	4+	4+	4+	4+	4+	—	—	—	—	—
7	4+	4+	4+	4+	4+	4+	4+	4+	—	—
8	4+	4+	4+	4+	4+	4+	—	—	—	—
9	4+	4+	4+	1+	—	—	—	—	—	—
10	4+	4+	2+	—	—	—	—	—	—	—
11	4+	4+	4+	4+	4+	4+	—	—	—	—
12	4+	4+	—	—	—	—	—	—	—	—
13	4+	4+	4+	4+	4+	4+	4+	—	—	—
14	4+	4+	4+	4+	4+	4+	4+	—	—	—
15	4+	—	—	—	—	—	—	—	—	—
16	4+	4+	4+	2+	1+	4+	4+	—	—	—
17	4+	4+	4+	4+	4+	—	—	—	—	—
18	4+	4+	4+	—	—	—	—	—	—	—
19	4+	4+	4+	4+	4+	4+	3+	—	—	—
20	3+	1+	—	—	—	—	—	—	—	—
21	4+	4+	4+	4+	4+	—	—	—	—	—
22	4+	4+	4+	4+	4+	4+	—	—	—	—
23	4+	4+	4+	4+	4+	—	—	—	—	—
24	4+	4+	4+	2+	1+	3+	—	—	—	—
25	4+	4+	3+	—	—	2+	—	—	—	—

TABLE 7.—COMPARISON BY TITRATION OF STRONG POSITIVE SPECIFIC BLOODS WITH THOSE OF GOITER PATIENTS WHO GAVE FALSE POSITIVE REACTIONS WITH TEST 1

Strong Positive Serums (Three Syphilitic Cases)				Goiter Cases (With False Positive Reaction in Test 1)			
Serum	A	B	C	Dilution	X	Y	Z
1:10 c.c.	4+	4+	4+	1:10 c.c.	4+	4+	4+
1:15 c.c.	4+	4+	4+	1:15 c.c.	4+	4+	4+
1:20 c.c.	4+	4+	4+	1:20 c.c.	4+	4+	4+
1:30 c.c.	4+	4+	4+	1:30 c.c.	4+	4+	4+
1:40 c.c.	4+	4+	4+	1:40 c.c.	4+	4+	4+
1:60 c.c.	4+	4+	4+	1:60 c.c.	4+	2+	1+
1:80 c.c.	4+	4+	4+	1:80 c.c.	2+	—	—
1:120 c.c.	4+	4+	4+	1:120 c.c.	—	—	—
1:160 c.c.	4+	4+	4+	1:160 c.c.	—	—	—
1:240 c.c.	4+	4+	4+				
1:320 c.c.	4+	4+	4+				
1:480 c.c.	4+	4+	4+				
1:640 c.c.	4+	4+	4+				
1:960 c.c.	4+	4+	4+				
1:1280 c.c.	4+	4+	3+				
1:1500 c.c.	4+	4+	3+				
1:1750 c.c.	4+	3+	2+				
1:2000 c.c.	4+	1+	2+				
1:2500 c.c.	4+	1+	—				
1:3000 c.c.	4+	—	—				
1:4500 c.c.	4+	—	—				
1:6000 c.c.	4+	—	—				
1:7500 c.c.	2+	—	—				
1:9000 c.c.	—	—	—				

one day and a negative reaction the next, (except possibly after the use of alcohol-Craig) for in the ordinary diagnostic test $\frac{1}{20}$ c.c. or more of blood is usually used. I have never encountered a blood which gave a real positive test (a four plus reaction in all five tubes) which became negative except after weeks or months of time or treatment. It has not been rare in my experience, however, for a four plus in test 1 with negatives in tests 2, 3, 4 and 5, to change after a week or so to a flat negative.

I might also point out (using Table 7 as an example) how needless it is to use in a diagnostic test an amount of serum much greater than about $\frac{1}{20}$ c.c. when it is possible to devise a technic so delicate that as little as $\frac{1}{6000}$ c.c. has been known to give a four plus reaction. The use of large amounts of blood serum unfortunately gives rise to sources of error due to anticomplementary bodies, natural antisheep amboceptor, etc. These sources of error are reduced when small quantities of the patient's serum are used in the tests.

THE INTERPRETATION OF POSITIVE, NEGATIVE AND DOUBTFUL REACTIONS

It seems that the nearest one can approach the ideal Wassermann test at present is, first, to employ one or more tests sensitive enough to come out four plus in a great majority of cases of syphilis; second, to employ one or more tests so coarse or insensitive that they will under almost no circumstances give a false positive; third, to employ an intermediate test which is reasonably delicate and reasonably coarse, and which can be observed and taken with a grain of salt. When tests are carried out in this way, clean cut definite information can be gained. Active syphilis can be excluded almost entirely (error very small) if every test comes out flatly negative. Syphilis is almost proven positively if every test results in four plus. Difficulty arises when the delicate tests are positive, and the coarse tests are negative. In this case syphilis is neither proven nor disproven. Such a reaction, according to my experience, must be termed "doubtful" or "suspicious" and had better be excluded from use in diagnosis. The diagnosis of syphilis in patients giving doubtful reactions of this sort is subject to smaller error if based entirely on history, physical examination, lumbar puncture or the therapeutic test.

SERUM TITRATIONS AS A GUIDE IN THERAPY

While in my own work I use the term strongly positive in discussing bloods which give four plus reactions in all five tubes, I realize that in order to determine the real strength of a positive blood and call it actually strongly positive one must titrate (Tables 2 and 3). This is of more value in following the treatment, however, than it is in making a diagnosis.

This paper deals primarily with the Wassermann test as a diagnostic measure. However, I cannot refrain from saying something about the value of serum titrations as a guide to treatment and the inadequacy of a simple diagnostic technic for this purpose. Tables 8 and 9 show how confusing the Wassermann results may be in judging the result of treatment unless titrations are made. I have followed this procedure as a routine for two years in the majority of specific cases under my care and the titrations are shown in Tables 8 and 9 as a typical example.

TABLE 8.—WASSERMANN RESULTS OF THE FIVE TUBE TEST IN A PATIENT UNDER TREATMENT FROM APRIL TO MARCH (ELEVEN MONTHS). NOTE ABSENCE OF APPARENT IMPROVEMENT AND COMPARE WITH TITRATION RESULTS MADE SIMULTANEOUSLY SHOWN IN TABLE 9

	April	June	July	Aug.	Oct.	Jan.	Feb.	March
0.4% cholesterinized antigen	4+	4+	4+	4+	4+	4+	4+	4+
0.2% cholesterinized antigen	4+	4+	4+	4+	4+	4+	4+	4+
0.2% cholesterinized antigen (2 U complement)	4+	4+	4+	4+	4+	4+	4+	4+
Acetone insoluble	4+	4+	4+	4+	4+	4+	4+	3+
Alcoholic extract	4+	4+	4+	4+	4+	4+	3+	1+

TABLE 9.—WASSERMANN TITRATIONS MADE SIMULTANEOUSLY WITH DIAGNOSTIC TESTS SHOWN IN TABLE 8. NOTE MARKED IMPROVEMENT WHICH WAS NOT SHOWN BY THE DIAGNOSTIC REACTIONS

Serum	April	July	Aug.	Oct.	Jan.	Feb.	March
1:10 c.c.	4+	4+	4+	4+	4+	4+	4+
1:15 c.c.	4+	4+	4+	4+	4+	4+	1+
1:20 c.c.	4+	4+	4+	4+	4+	4+	—
1:30 c.c.	4+	4+	4+	4+	4+	4+	—
1:40 c.c.	4+	4+	4+	4+	4+	4+	—
1:60 c.c.	4+	4+	4+	4+	4+	4+	—
1:80 c.c.	4+	4+	4+	4+	4+	4+	—
1:120 c.c.	4+	4+	4+	4+	4+	3+	—
1:160 c.c.	4+	4+	4+	4+	4+	1+	—
1:240 c.c.	4+	4+	4+	4+	4+	—	—
1:320 c.c.	4+	4+	4+	4+	3+	—	—
1:480 c.c.	4+	4+	4+	4+	1+	—	—
1:640 c.c.	4+	4+	4+	2+	—	—	—
1:960 c.c.	4+	4+	4+	—	—	—	—
1:1280 c.c.	4+	4+	4+	—	—	—	—
1:1500 c.c.	4+	4+	2+	—	—	—	+
1:1750 c.c.	4+	4+	1+	—	—	—	—
1:2000 c.c.	4+	3+	—	—	—	—	—
1:2500 c.c.	2+	1+	—	—	—	—	—
1:3000 c.c.	—	—	—	—	—	—	—
1:4500 c.c.	—	—	—	—	—	—	—

Table 8 shows Wassermann results obtained with the five tube diagnostic test previously described used on a patient under treatment at different dates (April to March). During this period of eleven months the patient was under antispecific treatment and improved clinically. It can be noted, however, that during this entire period tests 1, 2 and 3 were all unchanged. They were four plus in the beginning of treatment and four plus at the end of this period. Test 4 showed no change for eleven months when it became three plus instead of four plus.

Test 5 showed no change for ten months when it became less strongly positive. Should one have this chart alone he might wonder why this patient had not shown more improvement serologically during this period. Was he a Wassermann-fast case, an incurable cerebral case, or what? A different impression is gained from Table 9 which gives the result of serum titrations carried out simultaneously with the diagnostic tests. It shows that in April the patient gave a four plus reaction with $\frac{1}{2000}$ c.c. of serum; in August with $\frac{1}{500}$ c.c., in January with $\frac{1}{200}$ c.c., in February with $\frac{1}{100}$ c.c. and that in March $\frac{1}{10}$ c.c. of serum was required to give a four plus reaction. (I have chosen arbitrarily the set-up of test 3 for serum titrations). In other words, between July and February almost no improvement was shown serologically by the ordinary diagnostic tests (Table 8), whereas titrations disclosed the fact that the patient had only $\frac{1}{1000}$ the amount of complement fixing body in his blood in March as he had at the beginning of treatment. In other

TABLE 10.—EXAMPLE OF A SO-CALLED WASSERMANN-FAST CASE. SERUM WAS AT NO TIME INTENSELY POSITIVE. HOWEVER, IT WAS NOT MATERIALLY ALTERED DURING ELEVEN MONTHS BY MANY DIFFERENT PLANS OF TREATMENT. CASE APPEARS CLINICALLY TO BE ONE OF IMPENDING PARESIS

Serum	March	April	May	Aug.	Sept.	Dec.	Feb.
1:10 c.c.	4+	4+	4+	4+	4+	4+	4+
1:15 c.c.	4+	4+	4+	4+	4+	4+	4+
1:20 c.c.	4+	4+	4+	4+	4+	4+	4+
1:30 c.c.	4+	4+	4+	4+	4+	3+	4+
1:40 c.c.	4+	4+	4+	4+	4+	2+	4+
1:60 c.c.	4+	4+	4+	4+	4+	—	4+
1:80 c.c.	4+	4+	2+	2+	4+	—	2+
1:120 c.c.	3+	3+	—	—	2+	—	—
1:160 c.c.	1+	—	—	—	—	—	—
1:240 c.c.	—	—	—	—	—	—	—

words, instead of being serologically unfavorable, he was actually favorable, considering the fact that he was a late case. In following therapy be means of the Wassermann reaction, the occasional sending of blood to a laboratory or to several laboratories for Wassermann tests may give the poorest possible information concerning the results of therapy and concerning prognosis, unless the physician acquaints himself with the type and delicacy of the method used by his laboratory consultant. Both patient and physician can be unnecessarily discouraged and misled by the continued finding of a four plus reaction obtained by a sensitive method.

Repeated titrations on patients under treatment make the so-called Wassermann-fast case appear much less common. The blood illustrated in Table 9 would appear (falsely) to be Wassermann-fast if the diagnostic tests 1, 2 or 3 alone had been used. In Table 10 is shown what appears to be an example of a real Wassermann-fast case. This patient (with impending paresis) had been under treatment for months before

he came under observation. While under my care he showed practically no improvement, although many different plans of therapy were employed. Repeated tests made over a period of eleven months showed that the blood serum, although at no time intensely positive, was almost as strongly positive at the end as it was at the beginning of treatment (it gave a four plus reaction with $\frac{1}{60}$ c.c. of serum). In fact, at no time was the Wassermann reaction reduced to the point where less than $\frac{1}{20}$ c.c. would give a four plus reaction with test 3. Failure to improve serologically is a bad prognostic sign. A patient who persistently, and in spite of treatment, fails to improve serologically, or who improves while under treatment and quickly drops back (in from one to three months) when treatment is discontinued, does not do well eventually, as a rule.

SUMMARY AND CONCLUSIONS

The ideal Wassermann reaction is the result of a test sensitive enough to be positive in every case of active syphilis and negative in patients not afflicted with syphilis. Such a test, however, is a theoretical and practical impossibility. A test sensitive enough to be positive in the great majority of patients with late syphilis is, of necessity, so sensitive that it will be positive in a certain proportion of patients who do not have syphilis. On account of this I have used for several years a five tube test, two tubes of which I have endeavored to make delicate enough to give a positive result almost invariably in patients with active syphilis, two tubes so coarse or insensitive as virtually never to give a false positive, and one intermediate tube.

In this paper I have compared the clinical and serologic findings in a series of chronic medical cases to determine, if possible, the exact value and significance of both positive and negative reactions in each tube (set-up in the five different ways described previously). The most sensitive tube (cholesterinized antigen 0.4 per cent., one unit of complement, icewater bath incubation) was found by titration to be approximately eight times as delicate as the least sensitive one (alcoholic extract antigen, two units of complement, icewater bath incubation).

The tabulations showed that tube 1 (extremely sensitive) gave a four plus reaction in 95 per cent. of patients in whom syphilis could be demonstrated by other means; a one to three plus reaction was obtained in four of the remaining 5 per cent. of cases, and a flat negative was obtained in less than 1 per cent. It came out four plus in 31 per cent. of miscellaneous medical cases regardless of diagnosis. Of this 31 per cent. which gave positive tests, syphilis could be demonstrated by other methods in only 32.7 per cent. In other words, 67.8 per cent. were apparently false positives. Furthermore, it was found that of patients who gave a positive reaction in this tube with negative reactions with

the coarser ones, apparently 93.5 per cent. were false positives. A positive reaction with a test of this delicacy, therefore, is of no value whatever in the positive diagnosis of syphilis. A negative reaction, however, is very useful in its exclusion.

Tube 5, which was relatively insensitive (noncholesterinized antigen with two units of complement and icewater bath incubation) came out positive in 57 per cent. of patients who had syphilis which could be demonstrated by other means. Syphilis was proven positively in 98 per cent. of patients who gave a four plus reaction in this tube. No evidence of syphilis was found in the remaining 2 per cent. This might have been attributable, however, in part, to the circumstance that they were not examined adequately. A positive reaction with tests of this delicacy (only moderately sensitive) is believed, therefore, to be almost proof positive of syphilis. It is quite apparent, however, that a negative reaction could be of no value whatever in its exclusion.

The intermediate tube 3 (cholesterinized antigen 0.2 per cent. with two units of complement and icewater bath incubation) was less interesting and useful than the more extreme ones. It gave four plus reactions in 75 per cent. of patients with proven syphilis. It came out four plus in 8.5 per cent. of miscellaneous medical cases (including syphilis). Only 7.3 per cent. of this latter group of positives were false positives. Of the miscellaneous cases, however, which gave positive reactions in this tube with negatives in the less sensitive tubes (4 and 5), 30 per cent. were apparently false positives. The dependability of both positive and negative reactions obtained by a test of this delicacy, therefore, would appear to be practically nil.

The above statistics are of additional interest because of the fact that they were obtained almost entirely from a study of chronic late cases of syphilis.

Judging from the data recorded, it seems apparent that if extremely sensitive and reasonably coarse (or insensitive) tests are carried out simultaneously, valuable information can be gained not only concerning the positive diagnosis of syphilis but also concerning its exclusion. This divides medical cases into three classes, so far as the diagnosis of syphilis is concerned, namely, those in whom syphilis can be diagnosed positively by blood examination alone (that is when every test reacts four plus); those in whom the possibility of syphilis can be almost excluded by blood examination alone (that is when every test is negative), and those in which blood examinations are of no service whatever (that is when the sensitive tests react positive and the less delicate ones negative to three plus). In cases of this class the diagnosis or exclusion of syphilis must be based entirely on history, physical examination, lumbar puncture and therapeutic test.

False positive reactions with sensitive tests were obtained more frequently in individuals who were ill than it was in a series of healthy individuals who were tested as candidates to be donors for blood transfusion. It was also observed that false positive reactions of this type were obtained more frequently in patients who had goiter (regardless of size and toxicity) extreme ptosis, active tuberculosis, chronic sepsis, hypertension, pernicious anemia, diabetes and atrophic arthritis, than it was in individuals who did not have these diseases. In no instance, however, did patients with the above diseases in whom the possibility of syphilis could apparently be excluded, give four plus reactions with the less sensitive tests (4 and 5).

In following the results of treatment, simple diagnostic tests in our hands were misleading. The real progress of a patient can be followed much more satisfactorily, so far as serology is concerned, by the use of titrations.

I wish to acknowledge with pleasure the expert assistance in this work of Miss Elizabeth Leas, clinical laboratory assistant.

STUDIES IN ASYMPTOMATIC NEUROSYPHILIS

III. THE APPARENT INFLUENCE OF PREGNANCY ON THE INCIDENCE OF NEUROSYPHILIS IN WOMEN *

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In the second paper of this series [1] it was pointed out that in spite of the fact that clinical neurosyphilis is more common in men than in women, cytobiologic abnormalities in the cerebrospinal fluid of primary and secondary syphilitics are equally frequent in the two sexes. Futhermore, evidence was presented to show that from the group of patients showing these early fluid abnormalities (early asymptomatic neurosyphilis) arise most, if not all, of the late cases of clinical meningeal and parenchymatous neurosyphilis. Since women are comparatively exempt from clinical neurosyphilis, there must be some special factor, applying only to the female sex, which inhibits its development. It was suggested that pregnancy might be the factor in question. The purpose of this paper is to examine this point more in detail.

The literature is replete with statistics, dating from the earliest days of the study of syphilis, regarding the comparative incidence of neurosyphilis in the two sexes. The most complete are those recently published by Gärtner [2] on general paresis. He finds, on the basis of the incidence of paresis over a period of years in a population of about 38,000,000 Germans, that the ratio of paretic men to women is 3.43:1. Gärtner and other authors, notably Fournier,[3] suggest that this difference is largely due to the higher incidence of syphilis in men than in women, together with extraneous factors such as the greater stress of masculine activities.

Virtually, all women with acquired syphilis are within the child bearing period and are thus subject to any influence which pregnancy

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* From the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.

* This clinical research has been aided by grants from the United States Interdepartmental Social Hygiene Board and from the American Social Hygiene Association.

1. Moore, J. E.: Studies in Asymptomatic Neurosyphilis. II. The Classification, Treatment, and Prognosis of Early Asymptomatic Neurosyphilis, Bull. Johns Hopkins Hosp. **33**:231 (July) 1922.

2. Gärtner, W.: Ueber die Häufigkeit der progressiven Paralyse bei kultivierten und unkultivierten Völkern. Eine statistische, biologische, und Immunitätsuntersuchung über die Syphilis, Ztschr. f. Hyg. u. Infektionskr. **92**: 341 (July) 1921.

3. Fournier, A.: Les Affections Parasyphilitiques, Rueff et Cie, Paris, 1894, p. 168 et seq.

may exert. Congenital neurosyphilis, however, for example, juvenile paresis, develops in most instances before the child bearing age. In this condition, according to statistics gathered by Schmidt-Kraepelin,[4] both sexes are about equally affected, with only a slight preponderance of males.

Statistical data from the Syphilis Clinic of the Johns Hopkins Hospital are available for the examination of this problem. The clinic is for charity patients only. Its clientele is almost equally divided between the white and colored races. As to sex, there are about equal numbers of white and colored males, but colored females predominate over white women in the ratio of about 3:2. This racial distribution must be taken into consideration in connection with the percentage data given for the sex incidence of neurosyphilis. The comparative freedom of negroes from neurosyphilis [5] tends to distort the percentages somewhat in favor of the female sex. For the purpose of the present discussion, however, the question of race has been disregarded, since

TABLE 1.—THE INCIDENCE ACCORDING TO SEX OF VARIOUS TYPES OF SYPHILIS, AND ESPECIALLY NEUROSYPHILIS, BASED ON THE ADMISSION DIAGNOSES OF 5,410 SYPHILITIC PATIENTS

Diagnosis		Male			Female		
		Number of Cases	Per Cent. of Total Males		Number of Cases	Per Cent. of Total Females	
Early syphilis (primary and secondary)		1,069	36.60		604	24.77	
Late syphilis (tertiary)		722	24.29		643	26.37	
Neurosyphilis	Tabes	140	4.71	20.38	22	0.90	6.47
	General paresis	207	6.96		49	2.01	
	Meningeal	50	1.68		22	0.90	
	Vascular	33	1.11		7	0.28	
	Unclassified	175	5.88		58	2.37	
Latent syphilis		715	24.06		1,130	47.57	

both whites and blacks are subject alike to the factor of pregnancy. The social level of these patients needs little explanation. For the most part, they are unskilled laborers and their families.

Reference to Table 1 shows that of 5,410 patients with syphilis, 54 per cent. are males, 46 per cent. females. There is, thus, no great preponderance of syphilis in men in this class of patients. In order to emphasize the influence of pregnancy on the disease, all admission diagnoses have been tabulated. Marked sex variations are apparent in three of the four groups. The lower percentage of females with early syphilis is partly due to the anatomic difference in the sexes, with the consequent difficulty of detection of primary syphilis in the female. (Secondary syphilis is about equally frequent in the two sexes: 22.9

4. Schmidt-Kraepelin, T.: Ueber die Juvenile Paralyse, Monogr. a. d. Gesamtgebiete d. Neurol. u. Psychiat., Julius Springer, Berlin **20**: 1920.

5. Zimmerman, E. L.: A. Comparative Study of Syphilis in Whites and Negroes, Arch. Dermat. & Syph. **4**:75 (July) 1921.

per cent. males as against 21.5 per cent. females). No sex variation is evident in the incidence of tertiary syphilis. Latent syphilis, however, is twice as frequent in women as in men. This striking difference is due, together with part of the variation in the incidence of primary syphilis, to the effect of pregnancy on the course of the disease. No less than 470, or 42 per cent., of the women with latent syphilis, were pregnant on admission to the clinic.

The fact that women who bear syphilitic children often give no history of syphilis and present no signs of the disease (except a positive blood Wassermann reaction) has long been common knowledge. A study of the pregnant women in this clinic, now in progress, has convinced us that the usual early manifestations of syphilis are markedly altered by the occurrence of pregnancy. A woman infected at or shortly after the time of conception usually does not develop a chancre or secondary syphilis. When infection takes place late in pregnancy, on the other hand, the usual course of events may follow, but is often much delayed. Substantiation of these clinical data in experimental syphilis is furnished by the recent work of Brown and Pearce.[6]

If such striking alterations in the early course of the disease can be caused by a concurrent pregnancy, it is of great interest to examine the later course of syphilitic women who have been pregnant as contrasted with those in whom no pregnancy has occurred since infection. In the preceding paper of this series, it was shown that the incidence of spinal fluid abnormalities in 113 women with primary or secondary syphilis (examination of the fluid having been carried out, in most instances, within the first two years of the disease) was 22.1 per cent., as compared with 21.6 per cent. in a similar group of 217 men. None of these women were pregnant at the time of infection, and all had passed through the usual course of early syphilis. This is a satisfactory demonstration that in the early stages of the disease, when pregnancy can be excluded as a modifying factor, the nervous systems of both sexes are equally liable to invasion by the organism. In order to determine, therefore, the possible influence of pregnancy, late syphilis only (of more than one year's duration) should be chosen. There must be contrasted the incidence of clinical neurosyphilis and of spinal fluid abnormalities, first in women as compared with men, and second in a group of women who were pregnant at or since infection as compared with a group who have had no pregnancies.

In Table 1 it is shown that 20.38 per cent. of the cases in males were diagnosed as being clinically neurosyphilitic on admission, as

6. Brown, W. H. and Pearce, L.: On the Reaction of Pregnant and Lactating Females to Inoculation with Treponema Pallidum; A Preliminary Note, Am. J. Syph. **4**:593 (Oct.) 1920.

compared with only 6.47 per cent. of the females. For every case of neurosyphilis in the female, therefore, there are 3.13 cases in the male. Further analysis shows the following ratios:

Cerebrospinal syphilis (unclassed)..for 1 female, there are 2.48 males
Tabes dorsalis .....for 1 female, there are 6.36 males
General paresis .....for 1 female, there are 4.22 males
Meningeal neurosyphilis .....for 1 female, there are 2.27 males
Vascular neurosyphilis .....for 1 female, there are 4.71 males

These figures are more accurate than those usually given, since they are based on the total number of male and female patients with syphilis, rather than on neurosyphilitics only. With regard to the proportion of pregnant and nonpregnant females, data regarding this series are not available. Junius and Arndt,[7] however, to mention only one of many articles dealing with this point, state that from 47 to 49 per cent. of paretic women are sterile, as compared to 16 or 20 per cent. of childless women in the general population. These authors,

TABLE 2.—The Incidence of Spinal Fluid Abnormalities in Late Syphilis Without Evidence of Neurologic Damage: A Comparison of Men and Women

	Male			Female		
Diagnosis	Total Cases	Abnormal Fluids	Per Cent. Abnormal	Total Cases	Abnormal Fluids	Per Cent. Abnormal
II. Recurrent	8	2	25.0	4	—	0.0
II. Late	2	—	—	1	—	—
III. Skin and mucous membrane	30	8	26.6	39	3	7.8
III. Bone	40	5	20.0	31	4	12.9
III. Cardiovascular	38	7	18.4	10	2	20.0
III. Visceral	14	4	28.5	17	—	—
Latent	177	39	22.0	131	29	22.1
Total	309	65	21.03	233	38	16.3

and others, have all dealt with the subject from the standpoint of the influence of syphilis on child bearing, to show that syphilis causes sterility. So far as I am aware, it has not been suggested heretofore that pregnancy may alter the incidence of neurosyphilis in women, and that about half the paretic females may be paretic because of their sterility.

A further important point is the incidence of abnormal spinal fluids in late syphilitics without demonstrable neurologic abnormalities. For examination of this question 542 patients from this clinic are available. It is shown in Table 2 that of 309 men, 21.03 per cent. had abnormal fluids, as compared with 16.3 per cent. fluid abnormalities in 233 women. The percentage of abnormal spinal fluids in late syphilis of males is almost the same as the percentage in early syphilis (21.03 as

7. Junius, P., and Arndt, M.: Ueber die Deszendenz der Paralytiker, Ztschr. f. d. Ges. Neurol. u. Psychiat. **17**:303, 1913.

compared with 22.9). In women, on the contrary, spinal fluid changes are less frequent in late than in early syphilis (16.3 per cent. as compared with 22.1 per cent.).

If pregnancy is a factor of importance in causing this lowered incidence, those women with late syphilis who have been pregnant since their infection should show a lower proportion of abnormal fluids than those who have never been pregnant. That this is actually the case is shown in Table 3. Of ninety late syphilitic women who had never been pregnant, or had borne children only before infection with syphilis, 22.2 per cent. had abnormal fluids, while of 142 cases in which pregnancy had occurred one or more times after infection, only 11.2 per cent. were thus abnormal. The same phenomenon is observed whether tertiary manifestations of syphilis were present, or whether the disease was latent. The proportion of spinal fluid abnormalities in late syphilis, when no pregnancies have occurred, is thus precisely the same as that observed in early syphilis. In pregnant women, this percentage is reduced by one half.

TABLE 3.—THE COMPARATIVE INCIDENCE OF LATE ASYMPTOMATIC NEUROSYPHILIS IN WOMEN, SHOWING THE EFFECT OF PREGNANCY ON THE DISEASE

	Syphilis Contracted at Conception or Pregnant Since Infection			Never Pregnant Since Infection		
Diagnosis	Total Cases	Abnormal Fluids	Per Cent. Abnormal	Total Cases	Abnormal Fluids	Per Cent. Abnormal
Tertiary	54	2	3.7	44	7	15.9
Latent	89	14	15.6	46	13	28.2
Total	143	16	11.2	90	20	22.2

Included in the "pregnant" group are a considerable number of cases of conceptional syphilis—that is, infection with syphilis simultaneously with conception, and with consequent suppression of the early lesions of the disease. Thus a history of primary or secondary syphilis was obtained in only 21.8 per cent. of the patients in this group, as contrasted with 53.4 per cent. in the "never pregnant" group of women, and with 85.5 per cent. of males.

When infection with syphilis and pregnancy occur simultaneously, there can be no doubt that some factor in connection with the pregnancy inhibits the development of grave syphilitic lesions. This being so, one may ask if pregnancies occurring some time after infection confer the same sort of protection, and whether repeated pregnancies protect even more than a single one. As regards the former of these points, no information is at present available. In Table 4 is shown the percentage of abnormal spinal fluids in women who had had from one to five or more pregnancies since infection. There would seem to be

some protective influence exerted by repeated pregnancy, though the statistics are based on too small numbers and are, therefore, too irregular to be of much value. However, the percentage of abnormal fluids in those women who had two or more pregnancies is only 9.3, as compared with 19.5 in primiparae.

TABLE 4.—The Incidence of Late Aysmptomatic Neurosyphilis in Women, Grouped According to the Number of Pregnancies Since Infection

Number of Pregnancies	Total Cases	Abnormal Spinal Fluid	Per Cent. Abnormal
0	90	20	22.2
1	41	8	19.5
2	36	3	8.3
3	20	3	15.0
4	21	1	4.7
5 or more	19	2	10.5

It is not suggested that pregnancy occurring some time after infection, the woman having passed through the usual course of early syphilis, may exert any influence on the subsequent development of neurosyphilis. A larger series of cases than the present one is needed for examination of this point. Nor does the silent course of conceptional syphilis protect absolutely against later neurosyphilis. It is a well established clinical fact that in males, a mild early syphilis predisposes to neurosyphilis, possibly because of some alteration in the immune reactions of the body. In women, on the contrary, the factor of pregnancy in some way alters the defense mechanism so that the absence of early syphilitic lesions does not render the nervous system more susceptible to invasion. In this series, for example, spinal fluid abnormalities were present in 20.4 per cent. of eighty-three women, who, regardless of pregnancy, gave a definite history of primary or secondary syphilis, while of 161 women in whom such a history could not be obtained, only 13 per cent. had abnormal fluids.

CONCLUSIONS

1. Clinical neurosyphilis is about three times as frequent in men as in women.

2. The nervous systems of the two sexes are, however, invaded with equal frequency in the early stages of syphilis, as is shown by the relative percentages of spinal fluid abnormalities.

3. The course of early syphilis is markedly altered by the simultaneous occurrence of pregnancy.

4. Pregnancy is the most important point of difference in the ordinary life history of the two sexes.

5. In women with late syphilis (of more than one year's duration), the incidence of abnormal spinal fluids is twice as high in a group of sterile women as in a group in which one or more pregnancies have occurred since infection.

6. Almost half of the women who are clinically neurosyphilitic have not been pregnant since infection.

7. Multiparae seem to be less liable to late asymptomatic neurosyphilis than primiparae.

8. It is suggested on the basis of this study that pregnancy is one factor which may partially account for the comparative freedom of women from neurosyphilis.

THE SPECIFIC GRAVITY OF THE URINE*

T. ADDIS, M.D., AND MARJORIE G. FOSTER, M.D.
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The experiments reported in this paper were planned to determine whether there might not be certain special conditions under which the specific gravity of the urine could be used as a means for estimating the amount of secreting tissue in the kidney.

In 1914 Hedinger and Schlayer [1] described a method in which renal function was studied by observations of the specific gravity, volume, and chlorid content of collections of urine made at short intervals over a period of twenty-four hours. The modification of this test introduced by Mosenthal [2] has been used widely in this country. The interpretation of the results has given rise to much discussion but it has never been maintained that the test can be taken as a measure of the amount of renal tissue; in fact, Schlayer [3] has taken pains to point out that such an interpretation would be quite unwarranted. It would seem, then, that altogether other conditions than those hitherto used would have to be imposed if structural deductions are to be drawn from specific gravity changes in the urine.

Of course, it is evident, no matter what conditions are set, that the specific gravity by itself cannot be used for this purpose. It would have to be combined with a measurement of the volume of urine excreted during a definite period of time. The most that can possibly be learned from the specific gravity alone is the concentration of solids in the urine, and a concentration can never give information about the size of the kidney. This is sufficiently shown by the fact that the small kidneys of a child can produce as concentrated a urine as can be attained by the much larger kidneys of an adult. But if the specific gravity really does give the concentration of solids in the urine it can be used in conjunction with a determination of the rate of urine excretion to measure the amount of solids excreted per unit of time. This is a measurement which might very well be related to the amount of secreting tissue in the kidney.

There are two ways in which the capacity of the kidneys to produce a urine of high specific gravity may be put under strain. Fluids may be restricted, or the amount of solids calling for excretion may be increased. If both conditions were applied simultaneously it might be expected that a maximum effort of the concentrating capacity of the

* From the Department of Medicine of Stanford University Medical School.

1. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med. **114**:120, 1914.
2. Mosenthal: Arch. Int. Med. **16**:733 (Dec.) 1915.
3. Schlayer: Beih. z. med. Klin. **9**:211, 1912.

kidneys would be required. With this idea the effect of the ingestion of various solids on the specific gravity of the urine of subjects who were abstaining from fluids was observed.

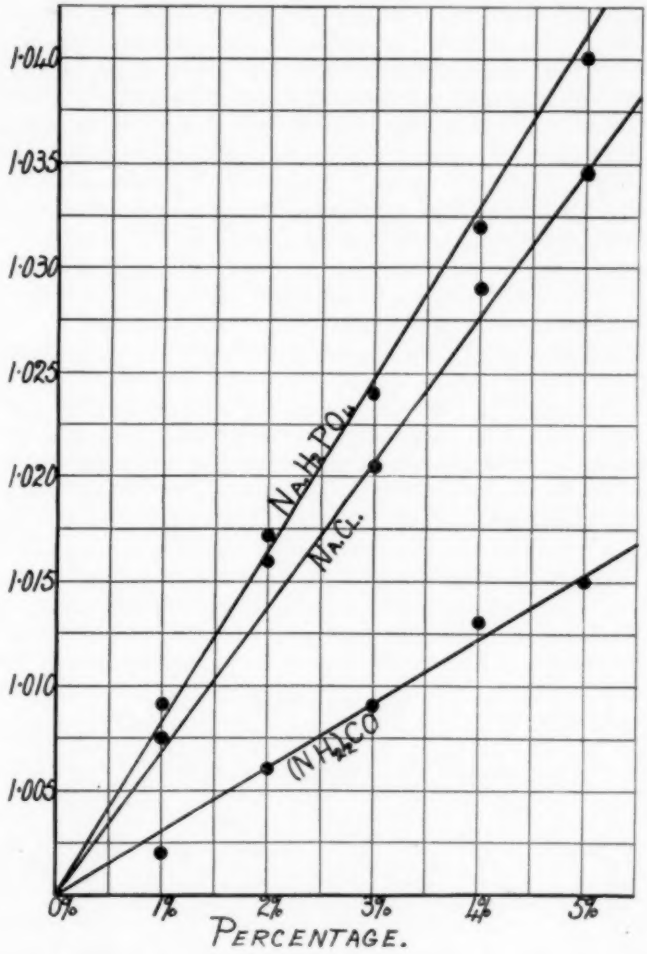
Five experiments were carried through on a group of ten students. In the first experiment the effect of simple fluid restriction was determined. For thirty-six hours no fluids of any kind were taken. The diet was quantitatively and qualitatively constant, and consisted mainly of starch and sugar. The protein and salt content was low, and all substances which might tend to increase the excretion of water through the kidneys were excluded. The collection of urine was started after twenty-four hours' abstention from fluids and covered the twelve hours of the night from 8 p. m. to 8 a. m. In the other experiments the same conditions were observed, except that at 8 p. m. various solids dissolved in 200 c.c. water were taken. In the second experiment, 30 gm. urea were used; in the third, 10 gm. sodium chlorid; in the fourth, 10 gm. sodium acid phosphate, and in the fifth, a mixture of 30 gm. urea, 5 gm. sodium chlorid and 5 gm. sodium acid phosphate was taken. The average specific gravities and volumes of the twelve hour night urines are given in the accompanying table.

AVERAGES FROM TEN NORMAL PERSONS UNDER FIVE DIFFERENT CONDITIONS

Conditions	Sp. G.	Volume in C.c.
Fluid restriction only	1.027	242
Fluid restriction and addition of 30 gm. urea in 15 per cent. concentration	1.025	597
Fluid restriction and addition of 10 gm. sodium chlorid in 5 per cent. concentration	1.028	391
Fluid restriction and addition of 10 gm. sodium acid phosphate in 5 per cent. concentration	1.035	213
Fluid restriction and addition of 30 gm. urea, 5 gm. sodium chlorid and 5 gm. sodium acid phosphate given in 200 c.c. water	1.025	616

Contrary to expectation, these figures show that the specific gravity of the urine is not greater after the addition of urea, sodium chlorid or a mixture of urea, chlorid and phosphate, than after fluid restriction alone. This is partially explained by the increase in urine volume which followed the administration of these substances, just as the relatively high specific gravity after sodium acid phosphate can, in part, be explained by the associated reduction in the volume of the urine. But the main point of interest lies in the fact that the specific gravity results cannot be accounted for fully by the urine volume changes. Their inadequacy can be shown by a consideration of the amounts of urea, chlorid and phosphate which were excreted. Thus, in the experiment with simple fluid restriction the total amount of all three substances was 8.44 gm. ($(NH_2)_2CO$, 5.40 gm.; + NaCl, 1.78 gm.; + NaH_2PO_4, 1.26 gm.). When the mixture was taken the total amount eliminated was 30.19 gm. ($(NH_2)_2CO$, 22.00 gm.; + NaCl, 4.63 gm.;

+ NaH_2Po_4, 3.56 gm.). It would be conservative to assume that these three substances together made up more than 75 per cent. of the total solids of the urine, and the remainder cannot have been far from constant since the urines were from the same group of subjects on a fixed diet. The figures 8.44 and 30.19 may be used as an indication of the



The specific gravity of varying concentrations of urea, sodium chlorid and sodium acid phosphate. The figure shows the wide differences between the specific gravities of equal concentrations of these substances. Thus 3 per cent. concentrations of urea, sodium chlorid and sodium acid phosphate have specific gravities of approximately 1.009, 1.020 and 1.024.

relative concentration of total solids in the two experiments. In the one case there is 8.44 gm. in 242 c.c., a 3.48 per cent. concentration of solids. In the other, there is 30.19 gm. in 616 c.c., a 4.90 per cent. concentration of solids. If the specific gravity of the urine depended only on the relation between the solids and the water in the urine, we should expect to find a higher specific gravity in a urine with 4.90 per cent. solids than in one with 3.48 per cent. solids. But the table shows that the reverse is true, for with 3.48 per cent. solids the specific gravity is 1.027 and with 4.93 per cent. the specific gravity is 1.025.

The explanation of this apparent paradox lies in the fact—known ever since the first specific gravity was measured—that each dissolved substance has its own specific effect on the specific gravity of a solution. This fundamental fact is generally ignored in discussions on the specific gravity of the urine, and, either tacitly or openly, it is assumed that the specific gravity measures the total concentration of solids.

Some rough determinations of the specific gravity of varying concentrations of urea, sodium chlorid and sodium acid phosphate are given in the accompanying figure.

This graph shows how it came about that the specific gravity of the urine was lower after taking a mixture of urea, chlorid and phosphate, than after simple water restriction, even though the total concentration of solids was greater. It was lower because a greater proportion of the total solids consisted of urea which has less effect in raising the specific gravity than chlorids or phosphates.

The specific gravity of the urine is the resultant of the various effects of all urinary constituents. Since each has its own specific effect and the relative concentrations are unknown, it follows that it is impossible to attach any precise quantitative significance to the results of any method of estimating the total solids of the urine in which specific gravity measurements are used.

CONCLUSIONS

The specific gravity of the urine of normal persons was measured under varying conditions designed to place a strain on the concentrating activity of the kidney. It was found that not even an approximate idea of the work of the kidney in the excretion of solids could be obtained from the results. It is therefore concluded that specific gravity determinations cannot form part of any method intended to measure the amount of secreting tissue in the kidney.

A TEST OF THE CAPACITY OF THE KIDNEY TO PRODUCE A URINE OF HIGH SPECIFIC GRAVITY*

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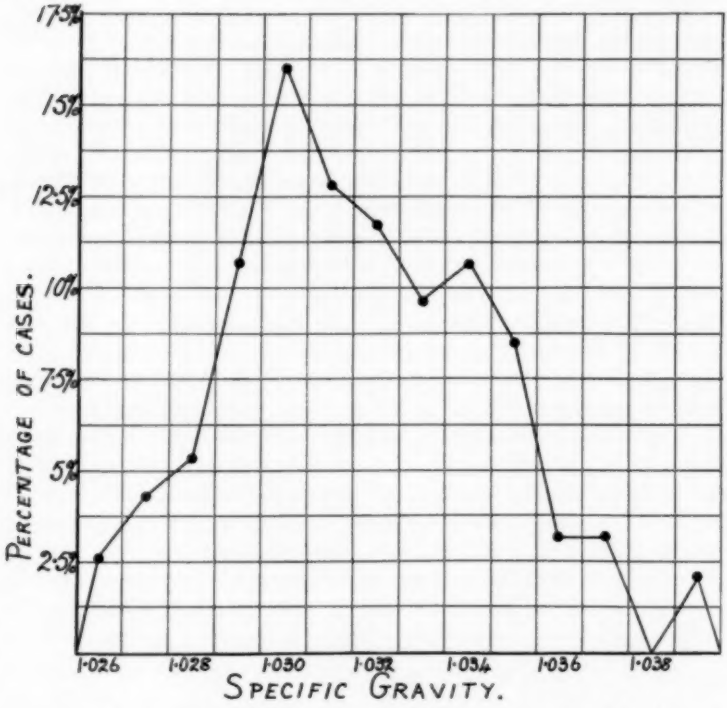
Although it has been shown in the preceding paper that the specific gravity of the urine cannot be used as a means to determine the rate of excretion of solids, and although it must be regarded as a very inaccurate method of estimating even that partial function of the kidney by virtue of which it is able to separate a concentrated solution from a blood in which the urinary constituents are relatively dilute, it, nevertheless, remains true that in certain cases specific gravity determinations may give information of considerable clinical value. There is a relation between the inability to produce a urine of high specific gravity and certain extreme grades of renal decompensation. It is this inability which, in certain cases, leads to the constantly low specific gravity in short time urine collections, which is in sharp contrast with the very variable specific gravity of the urine in normal persons. So many examples of this "fixation of specific gravity" at a low level have been given by Hedinger and Schlayer,[1] by Mosenthal,[2] and by Christian,[3] that it may be taken as a well established fact. And, on the other hand, so many far advanced cases of chronic Bright's disease are free or practically free from symptoms, that the demonstration of this inability may be the only indication of the real gravity of the situation in circumstances where only the simplest possible functional tests can be used.

But in this particular functional manifestation, as in all others, the clearest possible separation of normal from abnormal is only to be attained by making use of the principle of strain. This has not been done in the one day renal test of Hedinger and Schlayer, nor in Mosenthal's or Christian's modifications. For this reason, as well as for another given in a later paper, we have determined the variability of the specific gravity in normal persons under conditions specially designed to induce the production of a urine of high specific gravity.

In order that the test might be almost universally applicable, the conditions were made as simple as possible. The subject is instructed to abstain from fluids of all sorts after breakfast on one day until he rises from bed on the morning of the following day, and is told to

* From the Department of Medicine of Stanford University Medical School.
1. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med. **114**:120, 1914.
2. Mosenthal: Arch. Int. Med. **16**:733 (Dec.) 1915.
3. Christian: Oxford Med. **3**:585, 1921.

collect a twelve hours' night urine. In clinical work in the outpatient department we have found it necessary to give these directions in writing and to provide a wide necked bottle into which the urine is to be voided directly. It must be made plain that the urine passed at the beginning of the period of urine collection is to be discarded. The whole twelve hours' urine should be collected at one voiding, but if this is not possible the patient should be told not to pass urine for at



Percentage frequency distribution of specific gravity of the night urine in normal individuals after restriction of fluids.

least three hours before the completion of the specimen. The usual diet must be taken except that water, tea, coffee, milk, soup or any other fluid must be avoided. When these instructions are given fully, as well as clearly, it seems that few patients make mistakes.

We have made ninety-four observations on seventy-five normal persons, most of them medical students. The average is 1.032; the standard deviation ± .00281 and the variability 8.8 per cent. In the accompanying chart the percentage frequency distribution is given, and

in Table 1 the odds that any normal individual would have as low or a lower specific gravity than certain specified levels are tabulated.

TABLE 1.—The Odds That any Normal Individual Under the Conditions of the Test Would Give as Low or a Lower Specific Gravity Than Those Given Below

Specific Gravity	Odds
1.026	1 normal in 47
1.025	1 normal in 115
1.024	1 normal in 323
1.023	1 normal in 1,000
1.022	1 normal in 5,000

In these specific gravities from normal persons variations in the amount and the kind of food taken no doubt led to a somewhat greater variability than would otherwise have been found. But in patients a still greater variation in diet may be likely to occur, perhaps enough in some cases to make our normal figures inapplicable as a standard of comparison. The specific gravities of a few normals under the usual conditions and after taking from 1 to 1.5 pounds of steak with their evening meal were compared. Table 2 shows that there was no appreciable difference.

TABLE 2.—Comparison of Specific Gravities in Normals with Usual Diet and with Heavy Meat Diet

Name	Usual Diet	Usual Diet + 1 Pound or More of Steak at 6: 30 P. M.
B.	1.032	1.029
T.	1.027	1.026
L.	1.030	1.033
C.	1.028	1.029
N.	1.035	1.032
H.	1.035	1.030
Average	1.032	1.030

Some of our patients had been on a low salt and low protein diet before the test was used, and in normal persons this type of diet seems to make the specific gravity lower and more variable. Table 3 shows a comparison between specific gravities under the ordinary unrestricted dietary conditions and those obtained after the subjects had lived for forty-eight hours on food with a very low salt and a low protein content.

A specific gravity somewhat lower than normal obtained from a patient whose salt and protein intake has been restricted might then be due entirely to the diet. But even when the diet is unrestricted, low specific gravities in patients must always be interpreted with caution. There is the ever present possibility that the patient has not abstained

from fluids or has failed to discard the urine passed at the commencement of the twelve hour period. And, then, of course, there are many extrarenal factors in patients which may lead to an unusually large excretion of water and so to a low specific gravity, even though the

TABLE 3.—Comparison of Specific Gravities in Normals on Ordinary Unrestricted Dietary and on Very Low Salt and Low Protein Diets

Name	Usual Diet	Low Salt and Protein Diet
N.	1.035	1.020
W.	1.030	1.033
H.	1.035	1.029
L.	1.030	1.031
Wa.	1.032	1.027
T.	1.027	1.019
Average	1.032	1.027

concentrating capacity of the kidneys is unimpaired. On the other hand, there is never any doubt about the meaning of a high specific gravity, and it is here that the test has its main clinical value. For when a specific gravity within the normal range has been achieved a positive fact has been established which in itself is probably sufficient to exclude the possibility of the existence of that terminal stage of renal decompensation which so often develops insidiously in cases of chronic Bright's disease.

The specific gravities found in various types of renal lesion will be discussed and compared with other functional results in a later paper.

CONCLUSION

A simple test of the capacity of the kidney to produce a urine of high specific gravity is described. In normal individuals, after restriction of fluids, the average specific gravity is 1.032 with a standard deviation of $\pm$ .00281. These figures may be used as a normal standard for comparison with observations made on patients under the same conditions.

STUDIES ON BLOOD LIPOIDS

I. THE RELATION OF CHOLESTEROL AND PROTEIN DEFICIENCY TO BASAL METABOLISM *

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Cholesterol possesses many points in common with the fats and lipoids and is, therefore, usually grouped with these substances. Its presence in the blood seems to go hand in hand with that of the fats, and the quantitative relationship it bears to them is fairly constant. By virtue of this and the fact that it can readily be determined quantitatively, estimates of cholesterol are often used as a measure or index of the total fat content of the blood. The origin of the cholesterol of the blood is not definitely known; some of it is undoubtedly exogenous, and some endogenous. It is subject to marked fluctuations under a variety of conditions. In some it appears to be independent of external causes and definitely associated with metabolic disturbances, as in diabetes, nephritis,[1] etc. There also can be no doubt of the relation of the blood cholesterol to the glands of internal secretion, particularly the suprarenal (Rothschild et al.) and the thyroid (Luden[2]). The question arises whether the lipoid variations in distrubances of metabolism and internal secretion are incidental, or if a definite relationship between them can be established.

With these facts in mind, studies have been undertaken for the purpose of correlating basal metabolism and blood cholesterol findings in a group of cases in which both are subject to fluctuation. Thus, the study embraces cases of exophthalmic goiter, thyroid adenoma, nephritis and nephrosis, myxedema, menopause and related conditions. In addition, certain other conditions in which one or the other factor (basal metabolism or cholesterol) is disturbed, have been studied for purposes of comparison.

The cholesterol determinations have been made by the Bloor modification of the Funk-Autenrieth method. Because of the nature of this method, the personal equation constitutes an important factor. The majority of the determinations in our cases have been made by Dr. Joseph Reiss of our laboratory, who has analyzed more than twelve thousand specimens of blood; a sufficient experience to assure

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* From the Medical Department of Mt. Sinai Hospital.
* Read before the Section on Medicine, New York Academy of Medicine, Nov. 17, 1921.

1. Epstein, A. A.: J. A. M. A. **64**:444 (Aug. 11) 1917.
2. Luden, G.: Collected Papers Mayo Clinic **10**:429, 1918.

reliability and to warrant the conclusions which we shall draw from the results obtained. A survey of the figures of a very large series of examinations shows that the normal value for cholesterol in the blood ranges between 160 and 200 mg. per 100 c.c. By far the largest number show values nearer the upper limit.

The basal metabolism determinations have been made with the original Benedict portable apparatus. Oxygen consumption alone has been measured; a respiratory quotient of 0.82 having been assumed. Surface area has been estimated by the Du Bois-Du Bois height-weight formula. In those cases associated with edema, the weight used in calculation of the surface area was that which preceded the development of the edema, or followed its elimination. In this way, we believe, that the factor of tissue dilution has been eliminated from the estimations.

TABLE 1.—EXOPHTHALMIC GOITER

Acc. No.	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Remarks
					Calories	Per Cent.		
203475	K. C.	53	♀	Oct. 9	43.4	+20	0.230	
				Nov. 11	53	+46	0.130	
				Dec. 2	55	+54	0.150	
208738	S. M.	26	..	Mar. 26	43	+14	0.196	Postoperative
205137	D. R.	48	♀	Oct. 22	67.5	+82	0.090	
				Nov. 3	65	+78	0.080	
				Nov. 22	58.6	+62	0.140	
				Dec. 4	62	+72	0.095	
210167	M. M.	50	♂	Dec. 2	48	+28	0.136	
				Feb. 1	44	+15	0.182	
208597	A. A.	16	♂	Mar. 15	62	+37	0.148	
				Mar. 26	54.5	+25	0.178	
207946	M. F.	40	♂	Mar. 5	57	+46	0.166	
208189	N. J.	41	♀	Mar. 1	59	+63	0.130	
209330	F. B.	38	♂	April 15	61.5	+54	0.124	
209388	I. J.	23	♂	April 16	51.5	+30	0.106	
210372	M. H.	28	♀	May 22	52	+40	0.130	Gravid 3 months
210396	B. H.	30	♀	May 23	44.8	+20	0.136	
210814	I. K.	45	♂	June 11	66	+73	0.146	Chronic nephritis
				June 22	63.5	+65	0.130	
				June 25	....	....	0.156	
				Jan. 11	....	....	0.218	
211111	A. C.	40	♂	Jan. 12	49.5	+25	0.150	
212071	M. L.	28	♂	Sept. 1	48.5	+20	0.114	

Hyperthyroidism (Exophthalmic Goiter).—It will be seen that in all these cases (Table 1) the basal metabolism is increased, and the blood cholesterol figures are below normal. In general the decrease in the blood lipoid bears a direct relationship to the extent of increase of basal metabolism. In nine of the fourteen cases this holds true; the lowest metabolic figure, + 14 per cent., corresponding to a blood cholesterol of 0.196 per cent., and the highest figure, + 82 per cent., corresponding to a cholesterol of 0.090 per cent. This relation is not invariable, however. In three cases (I. J., B. H., and M. L.) the cholesterol figure is low in proportion to the increase of basal metabolism. These three cases are of two years' duration and it is not unfair

to assume an exhaustion of lipoid, which outlasted the elevation of the basal metabolism. The rising cholesterol figures in the case of I. J. are explained by a complicating nephritis. In the case of M. F. the cholesterol is higher than would be anticipated in a toxic case with a rate of + 46 per cent., and this discrepancy is not easily explained. Cases in which more than one determination has been made, however, show clearly that an inverse relationship exists between the metabolic rate and the cholesterol content of the blood, as was also found by Luden in a case of myxedema treated with thyroxin.[2]

TABLE 2.—NONTOXIC THYROID ENLARGEMENTS (ADENOMAS)

Acc. No.	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Remarks
					Calories	Per Cent.		
205905	A. G.	27	♀	Nov. 27	40	+ 6	0.162	
206087	L. R.	58	♂	Dec. 2	44	+15	0.162	
207838	J. B.	60	♂	Dec. 23	42.5	+12	0.184	
208589	A. K.	46	♀	Jan. 4	33.3	— 7	0.178	
	C. C.	27	♀	Jan. 4	33.3	— 8	0.180	
210912	F. F.	53	♀	May 17	38.5	+ 5	0.188	

In Table 2, six cases of thyroid enlargement without clinical signs of toxicity are tabulated. The blood cholesterol figures range from 0.162 to 0.188 per cent.; the basal metabolism from — 8 to + 15 per cent.; variations which may be regarded as ranging fairly within the normal.

TABLE 3.—TOXIC THYROID ENLARGEMENT (ADENOMAS)

Acc. No.	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Remarks
					Calories	Per Cent.		
204896	A. S.	40	♀	Oct. 19	40	+ 9	0.328	
				Nov. 1	42	+15	0.218	
				Nov. 20	45	+24	0.238	
				Dec. 9	36.8	Normal	0.278	Partial thyroidectomy November 29
204922	E. J.	45	♀	Oct. 17	50.2	+38	0.178	Auricular fibrillation
205312	M. S.	51	♀	Nov. 1	49.8	+38	0.120	
206947	A. P.	38	♂	Dec 16	47.3	+30	0.148	
208768	A. R.	46	♀	Mar. 26	49	+36	0.164	
209002	M. H.	46	♂	April 2	46	+18	0.130	
209661	C. T.	61	♀	April 29	56	+58	0.174	Moderate dyspnea
209878	S. M.	49	♀	May 12	53	+48	0.130	
212972	H. H.	48	♂	Sept. 1	53.3	+38	0.132	
213154	M. K.	49	♀	Sept. 8	52	+44	0.160	

In Table 3 the findings are recorded in ten cases of thyroid enlargement (adenomas) showing toxic signs clinically and an increase of basal metabolism. In only six of these does the inverse relationship as set forth above, between blood cholesterol and basal metabolism, hold true. In this group also, the cases in which the cholesterol factor is low and out of proportion to the metabolic rate, are of longer duration. There remain four cases in which the blood cholesterol is normal or only slightly diminished, in spite of an increased basal metabolic rate. It

will be noted that these four patients were women at the ages of 45, 46, 49 and 61, respectively; three of the four were at the climacteric period. A series of cases in the menopause will be presented later, which will show that women at this age are subject to a hypercholesterinemia. We may then assume that the inverse relationship still holds true, but in the group of thyroid enlargements, due to sex incidence and the age at which the toxic symptoms developed, the initial figure is higher. Fortunately, we were able to study a case (A. S.) of definite thyroid adenoma in which toxic symptoms developed while the patient was under observation. The basal metabolism gradually rose from +9 to +24 per cent. with a corresponding fall of blood cholesterol of from 0.328 to 0.238 per cent. At this stage a thyroidectomy was performed. Ten days later, the basal metabolism had fallen to normal and the cholesterol had risen to 0.276 per cent.

TABLE 4.—Clinical Diagnosis (?) Hyperthyroidism (?)

Acc. No.	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Diagnosis
					Calories	Per Cent.		
206107	B. S.	71	♀	Dec. 7	34	−3	0.353	Auricular fibrillation
206274	B. R.	35	♀	Dec. 11	36.6	Normal	0.100	Gastric neurosis
206318	A. F.	40	♀	Dec. 14	32.6	−10	0.218	Paroxysmal tachycardia
207886	R. B.	17	♀	Feb. 16	50	+15	0.170	(?) Hyperthyroidism
208144	L. L.	24	♀	Feb. 26	35.4	−5	0.218	Neurasthenia
210072	M. G.	42	♀	April 19	39.8	+8	0.296	Neurosis
210622	E. W.	9	♀	June 14	65	+14	0.218	Exophthalmos
211139	H. B.	26	♂	June 27	40.5	+2	0.314	Neurosis
211881	M. M.	56	♂	June 30	38	Normal	0.164	Gastric neurosis
213132	N. H.	40	♂	Sept. 8	40	Normal	0.276	
	M. L.	34	♀	Dec. 4	41	+8	0.189	Visceroptosis

The next group of cases (Table 4) comprises those in which a condition of hyperthyroidism was suspected clinically. These are, for the most part, functional disorders. In this group, the basal metabolism ranges from −10 to +15 per cent. Of these cases, the blood cholesterol is normal in six. In four cases there is an increase in the blood lipoid, the cause of which is not clear. In only one case (B. R.) is the cholesterol below normal. This case is one of gastric neurosis of several months' duration, in which all food was vomited immediately after eating. The patient was undernourished and in a debilitated state and it is in these factors that we must seek the explanation for the low lipoid content. This group stands in marked contrast to the true cases of hyperthyroidism with elevated basal metabolism (Table 1) all of which showed cholesterol values below normal. This does not yet establish the value of a low blood cholesterol as a positive aid in the diagnosis of thyroid disease, but, in the absence of other known factors that tend to produce a hypercholesterinemia (diabetes, menopause, pregnancy, nephritis and obesity), a blood cholesterol of normal or

increased value is strong evidence against the existence of a thyrotoxic state. It appears, however, that if repeated examination of the blood indicates a progressive decline of the cholesterol content in the absence of food insufficiency, Addison's disease, or uremia, the fact may be taken as presumptive evidence of the existence of a thyrotoxic condition. This is true even if the cholesterol value of the initial examination of the blood is above normal (Case A. S., Table 3).

TABLE 5.—Cases with Subnormal Basal Metabolism and Nephritis

Acc. No.	Name	Age	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Diagnostic Notes
				Calories	Per Cent.		
204853	Anna L.	14	Dec. 8	30.7	—18	0.904	Nephrosis
206071	Rose B.	27	Dec. 21	32	—15	0.394	Nephrosis; Wass. 4+
			Jan. 6	37.8	Normal	0.552	Had been on thyroid therapy
			Feb. 9	34.9	— 6	0.460	Antisyphilitic treatment
211792	Esther S.	33	Sept. 15	30	—18	0.370	Nephrosis
			Sept. 27	30	—18		
			Oct. 18	32.8	—10		
			Oct. 29	34.7	— 4	0.296	
207030	Yetta H.	44	Jan. 11	29.1	—19	1.350	Myxedema
			Feb. 8	....	....	0.725	On thyroid therapy
			Feb. 15	38.6	+ 6	0.206	On thyroid therapy
			Mar. 31	40	+10	.....	On thyroid therapy
			May 12	29	—19	0.680	Stopped thyro'd after leaving hospital
216441	Maud E.	29	Jan. 6	34.5	— 8	0.508	Nephrosis
			Feb. 11	32.6	—13	0.800	
217115	Ira S.	35	Feb. 8	33.4	—15	0.320	Nephrosis
207745	Yetta R.	28	Feb. 21	37.6	Normal	0.394	Chronic diffuse nephritis
206949	Pepple W.	54	Jan. 10	37.4	+ 6	0.412	Chronic diffuse nephritis
215385	Isidor T.	48	Dec. 7	41	+ 6	0.254	Hypertensive nephritis
216350	Hyman B.	39	Jan. 15	41	+ 6	0.140	Chronic nephritis
209679	Celia R.	22	April 24	33	—14	0.313	Myxedema
212870	Arthur S.	20	Dec. 1	22.7	—42	0.102	Inanition
	Rose Y.	21	Dec. 21	32	—15	0.130	Creatinism
206706	Frank S.	30	Dec. 30	44.2	+12	0.484	Nephrosis; pulmonary tuberculosis

Cases with a Subnormal Basal Metabolism (Table 5).—For many years it has been known that a low rate of metabolism exists in cases of hypothyroidism. More recently conditions of subnormal oxidation have been recognized, the relation of which to the thyroid gland is not clear. A group of unclassified cases with low basal metabolic rates has been reported from the Mayo Clinic. Aub and DuBois, in 1917,[3] reported a reduction in metabolism in cases of nephritis with edema and make the following statement: "The reduction of metabolism per square meter of body surface found in nephritic edema is sometimes very marked (from 27 to 40 per cent.) and points to some cause other than mere dilution of tissue or skin distention." One of us[4] has pointed out the possibility of a certain group of chronic nephroses being a metabolic disorder allied to a state of hypothyroidism. The existence

3. Aub, J. C., and DuBois, E.: Arch. Int. Med. **19**:865 (May) 1917.

4. Epstein, A. A.: J. A. M. A. **64**:444 (Aug. 11) 1917; M. Clinics N. America **4**:145 (July) 1920.

of a hypercholesterinemia of unusual degree in both nephrosis and myxedema was noted. Eppinger,[5] Volhard,[6] and more recently Behr and Waldrop[7] have reported the beneficial results of thyroid therapy in cases of edema of obscure origin. The relationship existing between these cases of nephrosis and the thyroid was demonstrated in a striking manner by the following case:

REPORT OF CASE OF NEPHROSIS DEVELOPING MYXEDEMA

History.—Yetta H., aged 44, first entered the hospital Sept. 25, 1916. Past history is of no importance, except that menopause developed at the age of 28. For four months prior to admission there had been gradually increasing edema with pain in the lumbar region, weakness and anorexia.

Physical Examination.—Marked generalized edema and pallor.

Admission Diagnosis.—Chronic nephritis.

Urine.—The urine contained heavy traces of albumin, hyaline and granular casts and a moderate number of white blood cells. No red blood cells.

Blood Chemistry.—Urea nitrogen, 21 mg. per hundred c.c.; incoagulable nitrogen, 56 mg. per hundred c.c.; cholesterol, 0.400 per cent. No basal metabolism studies were being made at Mt. Sinai Hospital at this time. Blood pressure, 105/80; phenolsulphonephthalein excretion, 48 per cent. in two hours. Blood Wassermann, negative.

Clinical Course.—For two weeks the patient was kept on a Karrell diet and then on a salt free diet. There was no subsidence of edema or increase of urinary output. October 11 she was put on a high protein diet. Within a week there was marked diuresis which continued until the edema had entirely disappeared, within three weeks of institution of treatment. She was discharged as a case of nephrosis relieved by high protein feeding. The albuminuria persisted.

Second Admission.—Jan. 15, 1921, four years and three months later, the patient entered the hospital for the second time. During the preceding year there had been increasing weakness, mental dulness, swelling of the face and lids and nocturia. On physical examination the patient presented the classical picture of myxedema. The skin was harsh, dry and scaly; the hair brittle and sparse. The speech was slow and mentality was dull. There was marked swelling of the face and lids, nonpitting edema of the extremities and the typical subcutaneous infiltrations of myxedema.

Urine: Albumin, heavy trace with many hyaline and granular casts.

Blood Chemistry.—Urea nitrogen, 18.2 mg. per hundred c.c.; incoagulable nitrogen, 37.6 mg. per hundred c.c.; uric acid, 2.3 mg. per hundred c.c.; creatinin, 1.9 mg. per hundred c.c.; cholesterin, 1.350 per cent.

Basal Metabolism: 29.1 calories—19 per cent. The phenolsulphonephthalein output was 45 per cent. in two hours.

On the basis of these findings, the patient was put on thyroid extract. Marked improvement of all symptoms followed, the basal metabolism returned to normal; the blood cholesterol diminished and the loss of 23 pounds in weight in four weeks was noted. The effect of thyroid on the metabolic rate and the blood cholesterol is shown in Table 5; the inverse ratio again holding true.

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5. Eppinger, H.: Zur Pathologie und Therapie des menschlichen Oedems, Berlin, 1917.

6. Volhard: Die Doppelseitigen Haematogenen Nierenerkrankungen, Berlin, 1918.

7. Behr, O., and Waldrop, C. P.: Semana méd. **28**:661 (June 9) 1921.

Summary.—A case presumably one of nephrosis, on first admission to the hospital responded to a high protein diet with the disappearance of the edema after failure of restricted diets. She returned four years later as a typical myxedema and is relieved of all symptoms by thyroid therapy.

The late development of myxedema in this case of nephrosis may be regarded by some as a coincidence. To us, myxedema represents the extreme stage of a defective metabolism which is similar in character to that occurring in nephrosis. The therapeutic results obtained in certain nephritides with the high protein diet (with and without the addition of thyroid), warrant the conclusion previously reached, that there are borderline cases, on one side of which are those with a clinical picture of nephrosis, and on the other side, the cases of myxedema. For reasons previously pointed out by one of us [4] nephrosis may be regarded primarily as a condition of defective protein metabolism, characterized chemically by hypercholesterinemia and reduced protein content of the blood serum.

REPORT ON BASAL METABOLISM STUDIES

Basal metabolism studies have therefore been made on ten cases of nephritis and nephrosis (Table 5).

CASE 1.—*History.*—Anna L., aged 14, had been subject to frequent attacks of tonsillitis. Tonsillectomy one year ago. Scarlet fever six years ago; so far as can be determined there was no complicating renal condition at the time. For the six months prior to entrance to the hospital there had been gradually increasing edema, dyspnea, frequency and nocturia.

Examination.—On admission the physical examination was noteworthy only for generalized edema. The urine contained large amounts of albumin, hyaline and granular casts. Blood pressure, 125/70; phenolsulphonephthalein output was 30 per cent. in two hours.

Blood Chemistry.—Urea nitrogen, 19.6 mg. per hundred c.c.; incoagulable nitrogen, 40.3 mg. per hundred c.c.; uric acid, 2.8 mg. per hundred c.c.; creatinin, 1.8 mg. per hundred c.c.; cholesterol, 0.904 per cent. Basal metabolism: 30.7 calories (— 18 per cent.).

Diagnosis.—On entrance a diagnosis of chronic diffuse nephritis was made.

Treatment.—The patient was put first on a Karrell diet, then on a carbohydrate and high protein diet successively, but apparently with little benefit. A salt free diet and diuetics (theobromin sodio-salicylate) reduced the edema somewhat, and the weight fell from 106 to 97 pounds, but no further removal of fluid could be effected, and conditions remained stationary. Two months after entrace a high protein diet was again instituted, and, in addition, small doses of thyroid extract were given. Within two weeks the edema had disappeared entirely and the weight had dropped to 85 pounds. The failure of the high protein diet at first was due to the fact that it was impossible to get the patient to eat because of her extreme illness. Albuminuria was present at the time of discharge.

CASE 2.—*History.*—Rose B., aged 27, whose past history is of no importance, had noticed for eighteen months an increasing swelling of the legs, thighs and external genitalia, pallor and nocturia.

Examination.—Pallor and generalized edema. Blood pressure: 110/70; phenolsulphonephthalein output was 45 per cent. in two hours. The urine contained large amounts of albumin, many hyaline and granular casts, but no

blood cells. The Wassermann was four plus. A Wassermann test made at the Beth Israel Hospital one year ago was negative.

Blood Chemistry.—Urea nitrogen, 22.4 mg. per hundred c.c.; incoagulable nitrogen, 47.8 mg. per hundred c.c.; uric acid, 2.4 mg. per hundred c.c.; creatinin, 1.6 mg. per hundred c.c.; cholesterol, 0.364 per cent. Basal metabolism: 32 calories (— 15 per cent.).

Treatment.—The patient was put on a high protein diet and thyroid extract. Within one week after institution of this therapy she began to void large amounts of urine and continued to do so for two weeks. At the end of this time the edema disappeared, the weight had dropped from 137 to 122 pounds, and the basal metabolism had risen to the normal value of 37.8 calories. Ten days after the disappearance of the edema neo-arsphenamin therapy was instituted, on the supposition that syphilis entered as an etiologic factor, but after four injections, at weekly intervals, it had to be discontinued because of increasing albuminuria. This patient was followed in the outpatient department for several months and recurring edema was readily controlled by thyroid.

This case is very similar to the one reported by Waldrop and Behr,[7] as a syphilitic nephrosis with generalized edema, anemia, and high blood lipoids developing in the secondary stage of syphilis, which proved refractory to antisyphilitic treatment, but responded to thyroid therapy with complete disappearance of the edema.

CASE 3.—*History.*—Esther S., aged 33, was admitted to the hospital, July 15, 1921. She had had pyelitis four and a half years previously; salpingitis one year ago. For months previous to admission there had been gradually increasing edema, ascites and hydrothorax.

Examination.—The urine contained three plus albumin, hyaline and granular casts. Blood pressure: 95/60; phenolsulphonephthalein excretion, 35 per cent. in two hours.

Blood Chemistry.—Urea nitrogen, 14 mg. per hundred c.c.; nonprotein nitrogen, 31.5 mg. per hundred c.c.; uric acid, 4.5 mg. per hundred c.c.; creatinin, 1.5 mg. per hundred c.c.; cholesterin, 0.375 per cent.

Treatment.—For the first two weeks the patient was put on a high protein diet but with no improvement, with rather a slight increase in edema, the weight rising from 153 to 157 pounds. She then was given a salt free low protein diet, with fluids limited to 500 c.c. and various diuretics (caffein, digitalis and theobromin sodio-salicylate). Her condition grew steadily worse, the edema increased rapidly and September 5 her weight was 175 pounds. During this period there was a fluid retention of from 150 to 400 c.c. daily. September 5, the high protein feeding was again instituted, at first with little improvement. September 14 examination showed a basal metabolism of 30 calories, a decrease of 18 per cent. below normal. Thyroid extract was then given. Within a week there was a diuresis and for the first time the fluid output exceeded the intake by from 350 to 500 c.c. daily. October 29, the patient weighed 142 pounds, the basal metabolism had risen to —4 per cent. and only a trace of albumin was being excreted in the urine.

CASE 4.—*History.*—Maude E., aged 29, had had a bilateral ovarectomy done ten years previously. Her present illness began about four months ago with swelling of the legs, arms and face.

Examination.—Generalized edema of moderate degree. Blood pressure: 110/70. The urine contained four plus albumin, hyaline and granular casts; the specific gravity was between 1.010 and 1.022; phenolsulphonephthalein, 30 per cent. in two hours.

Blood Chemistry.—January 6: Urea nitrogen, 18.2 mg. per hundred c.c.; incoagulable nitrogen, 39.5 mg. per hundred c.c.; uric acid, 2.5 mg. per hundred c.c.; creatinin, 1.1 mg. per hundred c.c.; cholesterin, 0.508 per cent. Basal metabolism: 34.5 calories (—8 per cent.).

Treatment.—A high protein diet and thyroid therapy was followed by the complete disappearance of edema within two weeks. At the same time there was a progressive diminution in the amount of albumin lost in the urine. Then, for some unknown reason, the intense albuminuria recurred, edematous swellings reappeared; the basal metabolism dropped to —13 per cent., and the blood cholesterol rose to 0.8 per cent.

It is evident from this relapse that the cause operative in this case had not been eliminated and that the therapy was inadequate. Increase in the dosage of thyroid resulted in amelioration of the condition, but the ultimate outcome is still in doubt.

CASE 5.—*History.*—Ira S., aged 35, had marked generalized edema twelve years previously, accompanied by diminished urinary output. Condition lasted one and a half years. He had a similar attack six years ago and again one year ago. One week before entrance he developed slight generalized edema which cleared up very quickly. He eats freely during these attacks.

Examination.—Negative; no cardiac hypertrophy or edema. Blood pressure: 105/68. Urine contains three plus albumin; hyaline and granular casts.

Blood Chemistry.—Urea nitrogen, 15.4 mg. per hundred c.c.; incoagulable nitrogen, 35.8 mg. per hundred c.c.; uric acid, 2.4 mg. per hundred c.c.; creatinin, 1.3 mg. per hundred c.c.; cholesterin, 0.320 per cent.; total serum protein, 4.3 per cent. Basal metabolism: 33.4 calories, —15 per cent.

The findings in this case are of special interest because they indicate that the depression in basal metabolism is not dependent on the presence of edema, but is one of the essential phenomena in this disease.

CASE 6.—*History.*—Frank S., aged 36, had a pulmonary tuberculosis of seven years' duration. For the last seven months there had been generalized edema, dyspnea and gastric distress.

Examination.—Extensive bilateral pulmonary involvement; marked edema. Blood pressure: 125/80. The urine contained large amounts of albumin, hyaline and granular casts. The phenolsulphonephthalein output was 25 per cent. in two hours.

Blood Chemistry.—Urea nitrogen, 18.2 mg. per 100 c.c.; incoagulable nitrogen, 38.5 mg. per hundred c.c.; uric acid, 1.7 mg. per hundred c.c.; creatinin, 1.3 mg. per hundred c.c.; cholesterol, 0.484 per cent. Basal metabolism: 44.2 calories, + 12 per cent. (afebrile course).

Sputum positive for tubercle bacilli.

Treatment.—This case was at first considered one of nephrosis and the patient was put on a high protein diet for two weeks with no improvement. The case was then complicated by the development of a tuberculous otitis media and mastoiditis. When this subsided, the patient was put on a Karrell diet. Within three days there was a diuresis and the edema disappeared within two weeks on a restricted diet. There was no elevation of temperature to account for the slightly increased basal metabolism.

CASE 7.—*History.*—Yetta R., aged 28, had scarlet fever in childhood. This was a typical case of chronic diffuse nephritis with slight edema. Blood pressure: 145/100. Hemoglobin, 29 per cent.; erythrocytes, 1,800,000. The urine contained albumin three plus, many hyaline and granular casts.

Blood Chemistry.—Urea nitrogen, 82.6 mg. per hundred c.c.; incoagulable nitrogen, 146.7 mg. per hundred c.c.; uric acid, 9 mg. per hundred c.c.; creatinin, 8.8 mg. per hundred c.c.; cholesterol, 0.290 per cent. Basal metabolism: 37.6 calories; normal.

Course.—An attempt to relieve the edema with the high protein feeding was unsuccessful. Other measures were also of no aid. The patient left the hospital unimproved.

Case 8.—*History.*—Peppie W., aged 54, for several months noticed failing vision, nocturia and weakness. Blood pressure: 180/95. No edema. Albuminuric retinitis. Phenolsulphonephthalein output was 45 per cent. in two hours. The urine contained albumin two plus, hyaline and granular casts.

Blood Chemistry.—Urea nitrogen, 18.2 mg. per hundred c.c.; incoagulable nitrogen, 52.5 mg. per hundred c.c.; uric acid, 1.7 mg. per hundred c.c.; creatinin, 1.1 mg. per hundred c.c.; cholesterol, 0.412 per cent. Basal metabolism: 38.6 calories, + 6 per cent.

Course.—The patient's condition remained unchanged on a restricted diet and she was discharged unimproved.

Case 9.—*History.*—Isadore T., aged 48. Past history of no importance. Present illness began six months ago with severe frontal and occipital headaches, vertigo and anorexia.

Examination.—Cardiac hypertrophy. Blood pressure: 235/130 and 244/135. The urine contained a faint trace of albumin and hyaline casts; specific gravity ranged between 1.016 and 1.022. The phenolsulphonephthalein excretion was 25 per cent. in two hours.

Blood Chemistry.—Urea nitrogen, 16.8 mg. per hundred c.c.; incoagulable nitrogen, 64 mg. per hundred c.c.; uric acid, 3.5 mg. per hundred c.c.; creatinin, 2.3 mg. per hundred c.c.; cholesterin, 0.254 per cent. Basal metabolism: 41 calories, +6 per cent.

Course.—The patient was put on a restricted diet with little change in his condition.

Case 10.—*History.*—Hyman B., aged 39. Nephritis eleven years ago and again six years ago. For the past three weeks there has been generalized edema of moderate degree accompanied by severe headaches, partial blindness and lumbar pain.

Examination.—Albuminuric retinitis; cardiac hypertrophy. Blood pressure: 220/140. The urine contained a trace of albumin, hyaline and granular casts. The specific gravity was 1.010. The phenolsulphonephthalein excretion was 3 per cent. in two hours.

Blood Chemistry.—Urea nitrogen, 36.4 mg. per hundred c.c.; incoagulable nitrogen, 73.7 mg. per hundred c.c.; uric acid, 3.3 mg. per hundred c.c.; creatinin, 5.2 mg. per hundred c.c.; cholesterin, 0.140 per cent. Basal metabolism: 41 calories, + 6 per cent.

Course.—There was no change in the condition of this patient while on a restricted diet.

Case 10 is unquestionably one of chronic interstitial nephritis and shows a normal basal metabolic rate. The first five cases are true nephroses and show a definitely decreased basal metabolism. The edema in Case 1 cleared up on a high protein diet and thyroid therapy after all other methods of relief had failed. Rose B. (Case 2) showed a remarkable diuresis following high protein and thyroid. The basal metabolism returned to normal coincident with the clinical improve-

ment, but the blood cholesterol remained practically unchanged. In spite of a 4 plus Wassermann, antisyphilitic treatment only aggravated the condition.

Esther S. (Case 3) at first showed no improvement with the high protein diet, low salt and low protein diet, restricted fluids and diuretics. Then, when thyroid was given in combination with a high protein diet, a remarkable diuresis followed, with rapid disappearance of the edema, and a loss of 23 pounds in four weeks. In this case, apparently, the patient was unable to utilize adequately the protein given until thyroid was administered.

Maude E. (Case 4) presented a typical case of nephrosis which at first responded to a high protein diet and small doses of thyroid. The subsequent relapse, we believe, was due to insufficient thyroid dosage or utilization. This case is still under observation.

Ira S. (Case 5) had a nephrosis in the nonedematous stage. The reduced basal metabolism and the chemical findings characteristic of this type of disease were present. This is of particular significance as it demonstrates that the lowered metabolism in this condition is not due to tissue dilution.

Isadore T. (Case 9) had an essential hypertension with secondary nephrosclerosis. The blood chemistry indicates moderate nitrogen retention and slight increase in cholesterol. The basal metabolism is normal.

Peppie W. (Case 8) and Yetta R. (Case 7) had a chronic diffuse nephritis. The blood chemistry is, in the main, like that of the hypertensive types of nephritis (chronic diffuse nephritis and nephrosclerosis) differing only in the presence of a hypercholesterinemia. We believe that the high blood cholesterol may be due to a lipoid mobilization following the loss of much albumin through the kidney, and therefore does not indicate necessarily a primary metabolic disorder. This is supported by the fact that the basal metabolism in these cases is normal.

Frank S. (Case 6) was regarded as having a nephrosis with a slightly increased basal metabolism. Here we have the complicating factor of tuberculosis. The failure of the high protein diet and thyroid therapy in addition to the increased basal metabolic rate suggests that this condition has a tuberculous basis, and that the nature of the renal disturbance was that of an amyloid kidney.

In 1917 Aub and DuBois [8] reported metabolic studies on ten cases of nephritis. Five of these were diagnosed as chronic interstitial nephritis and showed normal metabolic rates corresponding to our findings. The remaining cases of their group were diagnosed as chronic parenchymatous nephritis with edema and may be summarized as follows:

JOSEPH U.; scarlet fever five years before entrance. Generalized edema for three weeks previous to admission. The urine contained albumin three plus, hyaline, granular and pus casts. The blood pressure was 175/108-149/84. The blood chemistry: Urea nitrogen, 57.4 mg. per hundred c.c.; incoagulable nitrogen, 100 mg. per hundred c.c.; creatinin, 1.91 mg. per hundred c.c. Basal metabolism varied from —7 to +14 per cent.

The patient did well on a mixed diet of 1,500 calories, 5 gm. nitrogen, and hot air baths. Edema disappeared almost entirely. Was doing well when he suddenly became ill, developed pneumonia and died eleven days after the onset of the infection.

WILLIAM S., aged 27, for one year had a recurring edema. There was marked edema at entrance. The urine contained large amounts of albumin, hyaline and granular casts. Blood pressure, 178/90. The blood chemistry: Urea nitrogen, 17.3 mg. per hundred c.c.; nonprotein nitrogen, 41.7 mg. per hundred c.c. Basal metabolism, +4 per cent.

The patient improved steadily on a restricted diet.

ADAM P., aged 26, history of rheumatic fever. The urine contained large amounts of albumin, hyaline and granular casts. There was marked generalized edema. The blood pressure was 200/130. The blood chemistry: Urea nitrogen, 34.3 mg. per hundred c.c.; creatinin, 0.5 mg. per hundred c.c.; uric acid, 3.7 mg. per hundred c.c. Basal metabolism ranged from —10 to —13 per cent.

The patient improved on a restricted diet and hot air baths, with the disappearance of the edema within three weeks.

LEE H., aged 21. Past history was not obtained. Marked edema was present. The urine contained albumin three plus; many hyaline and granular casts. The blood pressure was 115/80. The blood chemistry: Urea nitrogen, 32 mg. per hundred c.c.; creatinin, 0.84 mg. per hundred c.c. Basal metabolism, —13 per cent.

This patient was put on a restricted diet; the edema continued to increase, the weight increased, and the basal metabolism dropped to —27 per cent. The patient died and postmortem aspiration of the pleural cavity and abdomen yielded a milky fluid containing very few cells.

EDNA S., aged 13, history negative except for mild sore throat. There was marked generalized edema. Blood pressure: 145/105. The urine contained large amounts of albumin and many hyaline and granular casts. The blood chemistry: Urea nitrogen, 14.5-22.6 mg. per hundred c.c.; nonprotein nitrogen, 19.7 mg. per hundred c.c. Basal metabolism: —40 per cent.

A restricted diet low in nitrogen was of no benefit. The edema steadily increased and the patient died.

No lipoid studies were made in these cases.

It will be noted that in the three cases with normal metabolic rates the edema disappeared on restricted diets. In the two cases with marked decrease in basal metabolism, the edema steadily increased on restricted diets and both patients died. We believe that these two cases of Aub and DuBois correspond to our Cases 1, 2 and 3, which we regard as cases of true nephroses and which have yielded to high protein therapy. That our assumption of a respiratory quotient of 0.82 does not invalidate our basal metabolic determination in these cases is also shown by those observers. In twelve of their fourteen observations on nephritis the respiratory quotient ranged from 0.78 to 0.84. In only two cases were there abnormal values and these patients were on carbohydrate diets.

Basal metabolism studies on this group of cases have been undertaken only recently, and because of this, the number of cases reported is still relatively small. However, they gain added significance from the results of thyroid therapy recently reported by Epstein,[4] Eppinger,[5] Volhard[6] and others, in the treatment of various forms of edema, particularly war edemas, and others in which the factor of protein deficiency enters. The cases reported above show that those which respond to protein therapy are accompanied by a subnormal basal metabolism. This seems to us to be a logical finding in view of the associated defective protein metabolism, and may be explained by the diminution of the specific dynamic energy normally imparted by the products of protein catabolism. In this way the basal metabolism determination serves as an indirect measure of the protein deficiency, and may be an added diagnostic and therapeutic index of considerable value. That the beneficial effect of thyroid is due entirely to its stimulative influence on basal metabolism is open to question, and it is quite probable that its effect in promoting the utilization of exogenous and endogenous protein, as demonstrated by Magnus-Levy, von Norden et al., explains its action. This phase of the subject, however, is still a matter for further investigation; but that a low metabolic rate in itself is not sufficient to cause edema is shown by the following two cases:

Case 11.—Arthur S., aged 20, a psychopath who on a self-imposed low calory, low protein diet reduced his weight from 146 to 73 pounds.
Basal metabolism: 22.7 calories, —42 per cent. Blood cholesterol: 0.102 per cent.

Case 12.—Rose Y., aged 21, a cretin; on thyroid therapy and under observation for fifteen years. Symptoms entirely neurologic.
Basal metabolism: 32 calories, —15 per cent. Blood cholesterol: 0.130 per cent.

Neither of these patients developed at any time either edema or myxedema. It will be noted that these are the only two instances in which a low metabolic rate is associated with a low blood cholesterol, indicating the importance of increased lipoids as an accessory factor in edema. In these cases with a low basal metabolism the protein utilization is apparently unimpaired; a factor considered by Rubner as significant in the prevention of edema in cases of starvation. Further, it is of interest to note that in hyperthyroidism, a condition in which emaciation of great degree may occur, but in which the basal metabolism and protein utilization are increased, edema is practically never encountered.

In Table 6 ten menopause cases are reported. All have normal basal metabolic rates, but the blood cholesterol figures range from 0.182 to 0.394 per cent. The tendency to a hypercholesterinemia is noted in these cases. In this connection we wish only to point out the importance of the climacteric period as a factor in the elevation of blood

TABLE 6.—Menopause Cases

Acc. No.	Name	Age	Date	Basal Metabolism		Blood Cholesterol, Per Cent.
				Calories	Per Cent.	
208950	A. M.	42	April 15	42	+15	0.182
208982	G. L.	47	Mar. 31	40	+12	0.230
208949	Y. A.	40	Mar. 31	37.8	+ 3	0.192
209157	S. K.	48	April 7	39.8	+10	0.248
209174	C. B.	45	April 7	40	+10	0.220
209242	A. R.	40	April 11	38	+ 4	0.206
209169	E. F.	47	April 18	36	Normal	0.394
209561	A. F.	45	April 21	36.5	Normal	0.182
209671	H. W.	45	April 25	37.5	+ 4	0.240
209648	Y. R.	42	April 25	37	Normal	0.242

cholesterol, so that no false conclusions will be drawn in cases at this age with subnormal basal metabolism.

In Table 7 are recorded conditions in which either the blood cholesterol or the basal metabolism is subject to variation. These cases are too few to permit the drawing of any conclusions, but it will be seen that the inverse relationship between basal metabolism and blood cholesterol holds true in most of them, with the exception of the blood conditions.

TABLE 7.—Miscellaneous Group

Acc. No.	Name	Age	Sex	Date	Basal Metabolism		Blood Cholesterol, Per Cent.	Diagnosis
					Calories	Per Cent.		
211699	B. E.	20	♀	Oct. 21	37.8	Normal	0.218	Cholelithiasis
205390	D. R.	35	♀	Nov. 10	37.5	Normal	0.178	Cholelithiasis
206132	S. K.	49	♀	Oct. 23	36	Normal	0.130	Pernicious anemia
205808	A. M.	49	♂	Dec. 2	43	+10	0.236	Lymphatic leukemia
208909	S. K.	30	♂	Mar. 29	42.5	+ 7	0.084	Polycythemia vera
207396	B. A.	42	♀	Feb. 15	38.6	+ 6	0.284	Obesity
204394	E. C.	19	♂	Oct. 2	35	− 8	0.308	Hypopituitarism and glycosuria
208255	C. H.	25	♀	Mar. 12	40	+ 6	0.160	Achondroplasia
208109	M. B.	42	♀	Mar. 3	36.4	Normal	0.174	Splenomegaly with anemia
206713	H. G.	17	♀	Dec. 28	55	+32	0.100	Gaucher splenomegaly

DISCUSSION

The material presented, we believe, shows that the relationship existing between the metabolic rate and the blood cholesterol in thyroid disease is more than an incidental one. The low blood cholesterol values with an increased metabolic rate and the high values with a depressed basal metabolism, lead one naturally to believe that it may be only a matter of combustion; an increased rate of oxidation causing increased consumption of available lipoid, and vice versa. We do not believe that this is the complete explanation. However, until more is known about the metabolism of lipoids in the body, any explanation must be based on hypotheses, as yet incapable of proof. The more recent work of Marine and Bauman,[8] in which they demonstrated a

8. Marine, D., and Bauman, E. J.: Am. J. Physiol. **57**:135, 1921.

rise in basal metabolism following the destruction of the suprarenal cortex in rabbits, is especially suggestive, in the light of the close relationship existing between the suprarenal cortex and the blood cholesterol. Marine and Bauman suggest that the suprarenal cortex may have an inhibitory function in the regulation of basal metabolism. The possibility exists that such a power may be inherent in its lipoid content which is known to vary with that of the blood.[9] In Addison's disease, for example, the blood cholesterol is very low. It is also known that in fatal cases of exophthalmic goiter the lipoid content of the suprarenal cortex is greatly reduced.

Wasting diseases other than hyperthyroidism are associated with a low blood cholesterol. The diagnostic value of a low cholesterol is doubtful, but a normal or elevated figure must be a rare finding in exophthalmic goiter. In enlargements of the thyroid with toxic symptoms the lipoid content may be out of proportion to the metabolic rate, but this is explained by the menopause factor which tends to give a higher initial figure. Once established in connection with the basal metabolic rate, we believe that repeated cholesterol determinations offer a satisfactory method of following the course of thyroid toxicity. This is of special value in judging the effect of thyroid therapy in myxedema and allied conditions of hypothyroidism. It is known that in some cases of hyperthyroidism, the basal metabolism does not correspond to the severity of the condition as observed clinically. This is to be expected as the damage to the myocardium, nervous system and body reserve outlasts the elevation of the metabolic rate. We believe that in these cases the blood cholesterol, as an index of the lipoid content of the suprarenal cortex and body tissue, may be of considerable value in prognosis, and as an indication of the safety of operative procedure. It is worth noting that the patient with a blood cholesterol of 0.095 per cent. died on the operating table.

In nephrosis, we believe basal metabolism determinations will prove to be of great value in differentiating cases suitable for high protein and thyroid therapy. The subnormal metabolism found in these cases is not necessarily due to a hypothyroidism but to defective protein metabolism, with its associated diminution of the specific dynamic energy normally imparted by products of protein catabolism. In this way the basal metabolism determinations serve as an indirect measure of protein deficiency. We believe that the beneficial effect of thyroid is not due entirely to its stimulative action on the rate of oxidation, as a subnormal metabolism in itself is not sufficient to produce edema. The effect of thyroid in promoting the utilization of protein probably explains its ultimate influence on edema.

9. Rothschild, M. A.: New York Path. Soc. **14**: (Oct.) 1914.

THE DISTRIBUTION OF METABOLITES IN THE BLOOD AND TISSUES*

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MINNEAPOLIS

INTRODUCTION

With the introduction of simple and reliable microchemical methods of analysis, the determination of the concentration of metabolites in the blood has become an accepted clinical procedure. Consequently, the relation of metabolites in the blood to their distribution throughout the entire organism is a subject of clinical as well as theoretic interest. I wish here to consider the distribution of metabolites in the body as a whole in relation to their concentration in the blood.

Three methods have been applied in studying metabolite distribution. The first, which is used in this report, consists in parallel determinations of the metabolites in the blood and in the various body fluids. The second method consists in the postmortem analyses of tissues to determine their respective metabolite content. The third method is the study of the effect produced by the ingestion of a given quantity of meat, or urea, and the resultant changes in the blood metabolites, controlling the experiments with nitrogen excretion determinations. The limitations of each of these three methods will be discussed later.

The first parallel analyses of urea were made by Javal and Adler [1] in 1906, using the hypobromite method. In four cases they found the urea content of different fluids from the same cases in practical accord. Javal and Boyet [2] reported ten cases with a similar agreement in 1910. In 1911, Javal [3] made parallel urea estimations on the blood and cerebrospinal fluid in eighteen cases, blood and edema fluid in four cases, pleural and edema fluid in one case, blood and pleural fluids in five cases, and pleural and cerebrospinal fluids in five cases. The urea concentrations in the fluids from the same cases were virtually identical. Javal concluded that "when the urea increases in the serum it also increases simultaneously in the organism and diffuses through all the fluids of the organism in the same concentration in which it occurs in the serum. . . . The blood contains from 30 to 35 mg.

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1. Javal and Adler: Séances et Mém. de la Soc. de Biol. **61**:235, 1906.
2. Javal and Boyet: Ibid. **68**:527, 1910.
3. Javal: J. de phys. et de path. gen. **13**:508, 1911.

urea nitrogen per hundred cubic centimeters. Normally, the cerebrospinal fluid contains about the same quantity." Javal's figures are approximately twice those now considered normal for blood urea nitrogen, doubtless because the hypobromite method used gives nitrogen other than urea nitrogen added to the true urea nitrogen figure.[4]

Rosenberg,[5] in 1914, made parallel determinations of urea, creatinin and indican in the blood and in the ascitic, pleural, and cerebrospinal fluids of nephritics. He also used the hypobromite urea method. Normal subjects were not studied. Rosenberg concludes that "in uremia, the urea content of the pleural and peritoneal fluids is from 80 to 100 per cent. of the blood. The creatinin content is up to 20 per cent. of the blood, and the indican is equal to the blood. The cerebrospinal fluid contains from 56 to 96 per cent. of the urea content of the blood, and from 37 to 75 per cent. of the blood creatinin." With the exception of considerably higher creatinin percentages for the body fluids, these findings coincide with those reported here. Using modern microchemical methods, Bernhard [6] found the nonprotein nitrogen, urea nitrogen, sugar and chlorides in eleven transudates and exudates to be comparable to those of normal blood. He did not make parallel analyses of the blood at the same time, and does not state whether or not the fluids were obtained with the patient in the fasting state.

The sugar content of transudates and exudates compared to the sugar content of the blood at the same time has been studied by Hagler and Schumann,[7] using the method of Bang. Of six pleural transudates, all but one had as high a sugar content as the blood, or higher. In twenty pleural exudates, the sugar content was usually lower than that of the blood; in eight peritoneal transudates it was slightly higher, and in seven cases of peritonitis it was slightly lower than the normal blood sugar. The ingestion of 100 gm. levulose or dextrose caused parallel increases in the sugar content of blood and fluids. From parallel analyses on the blood and fluids in five cases with pleuritic, and four cases with ascitic effusions, Dennis and Minot [8] conclude that the urea, uric acid, creatinin and nonprotein nitrogen occur in the same concentration in exudates and transudates as in the blood. They found the sugar content of the four ascitic fluids somewhat higher than that of the blood, contrary to the pleuritic fluids, which had a somewhat lower sugar content.

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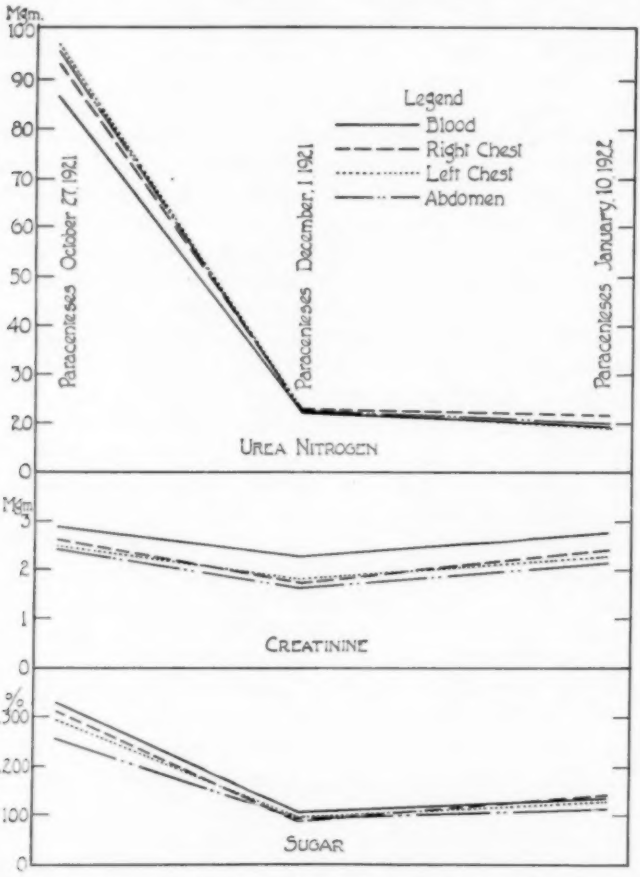
4. Herter and Wakeman: J. M. Research **4**:119, 1899; Johns Hopkins Hosp. Rep. **9**:69, 1900.
5. Rosenberg: Berl. klin. Wchnschr. **49**:1314, 1916.
6. Bernhard: Interstate M. J. **49**:188, 1918.
7. Hagler and Schumann: Med. Klin. **9**:1810, 1913.
8. Dennis and Minot: Arch. Int. Med. **20**:879 (Dec.) 1917.

Seham and Nixon [9] have recently investigated the chemistry of normal and pathologic spinal fluids. Their complete summary of the extensive literature makes further citation unnecessary. They report an average spinal fluid sugar content of 56.2 per cent. of the blood sugar in



Case of chronic nephritis illustrating parallel distribution of urea nitrogen, creatinin and sugar in the blood, ascitic fluid and right and left pleural effusions.

normal cases, with a maximum of 70.3 per cent. and a minimum of 47.8 per cent. Their findings for sugar are comparable to those of previous investigators. In four normal subjects they found the spinal fluid

9. Seham and Nixon: Arch. Int. Med. **28**:561 (Nov.) 1921.

creatinin to average 95.5 per cent. of the blood creatinin, and the diseases with high blood creatinin exhibited a corresponding increase in the creatinin content of the spinal fluid. In four normal subjects the urea content of the spinal fluid averaged 62.15 per cent. of the blood urea, with a range of from 45.5 to 174.6 per cent. in pathologic cases. Their findings for urea differ from those of Cullen and Ellis,[10] who report almost complete agreement between the urea content of the spinal fluid and the blood. Meyers and Fine [11] found in nephritics that the former averages 88 per cent. of the latter. The figures of Seham and Nixon are somewhat higher for spinal fluid creatinin, and somewhat lower for urea, than those reported in this paper.

The various investigators of the metabolite distribution between the blood and other body fluids thus appear in fairly close agreement. They find both the nitrogenous metabolites and the sugar in approximately the same concentration in fluids and in blood. The percentages for the blood are usually slightly higher than for the other fluids, but an increase in the blood values appears to be associated with corresponding increases in the values in the fluids.

PROCEDURE

This study is concerned with further investigation of the distribution of metabolites between the blood and other body fluids, primarily in cases in which the blood exhibits no retention of metabolites. A few cases with increased retention are included for comparison.

In all cases the blood and fluids were obtained simultaneously. The patients were kept without food overnight, and the samples were obtained before breakfast, Jacobsen and Edwards [12] having shown that there may be an increase in blood urea, as well as blood sugar, following the ingestion of an ordinary meal. The specimens were immediately sent to the laboratory, where parallel determinations of the sugar, urea nitrogen and creatinin were done. Most of the determinations were made in less than half an hour after withdrawal of the fluids from the patient. The analyses were all made by the same person. Double estimations on the same specimen were frequently made to check the technic, with results well within the limits of experimental error. Urea nitrogen was estimated by Van Slyke and Cullen's modification of Marshall's urease method,[13] creatinin by the method of Folin,[14] sugar by the method of Lewis and Benedict.[15] A Kober colorimeter was

10. Cullen and Ellis: J. Biol. Chem. **20**:511, 1915.
11. Meyers and Fine: J. Biol. Chem. **37**:239, 1919.
12. Jacobsen and Edwards: Am. J. M. Sc. **159**:579, 1920.
13. Van Slyke and Cullen: J. Biol. Chem. **24**:117, 1916.
14. Folin: J. Biol. Chem. **17**:475, 1914.
15. Lewis and Benedict: J. Biol. Chem. **20**:61, 1915.

employed. The percentage concentration of the metabolites in each fluid was obtained by dividing the concentration of the metabolite in the fluid, times 100, by the concentration of the metabolite in the blood.

CLASSIFICATION OF MATERIAL

In all, fifty-five fluids from thirty-six cases were analyzed. As often as possible, more than one fluid was obtained from the same case. Several cases were used more than once, but at each fluid determination a parallel blood analysis was done at the same time. The

TABLE 1.—CLASSIFICATION OF CASES ACCORDING TO GROUPS

Group			Cases
I	Effusions in cases with normal blood metabolites		31
	Ascitic transudates	13	
	Thoracic transudates	7	
	Ascitic exudates	4	
	Thoracic exudates	7	
II	Effusions in cases with increased blood metabolites		4
	Ascitic transudates	1	
	Thoracic transudates	3	
III	Cerebrospinal fluids in cases with normal blood metabolites		15
	Normal fluids	7	
	Pathologic fluids	8	
IV	Cerebrospinal fluids in cases with increased blood metabolites		5
	Normal fluid	1	
	Pathologic fluids	4	
Total			55

TABLE 2.—GROUPING OF FLUIDS ACCORDING TO CLINICAL DIAGNOSES

Diagnosis	Cases	Diagnosis	Cases
Chronic nephritis	10	Polyserositis	1
Hepatic cirrhosis	9	Acute peritonitis	1
Carcinoma	4	Acute pericarditis	1
Tuberculous pleurisy	4	Cholecystitis	1
Tabes dorsalis	3	Neurasthenia	1
General paresis	3	Dementia praecox	1
Myocardial degeneration	2	Neurosyphilis	1
Tuberculous peritonitis	2	Lethargic encephalitis	1
Empyema	2	Cerebrospinal meningitis	1
Hysteria	2	Uremia	1
Aneurism	1	Alcoholism	1
Hydrocele	1	Normal	1
Total			55

cases have been arranged in four groups (Table 1). The clinical diagnoses are arranged in Table 2.

EXPERIMENTAL RESULTS

The results of the determinations are given in Tables 3 to 8, and for comparison the average figures for each group are arranged in Table 7. In the cases with normal blood metabolite concentration, the sugar content of the ascitic transudates averaged 96.47 per cent. of the blood sugar, with a minimum of 51 per cent. and a maximum of 112 per cent. In the same cases the average ascitic urea nitrogen was 95.90 per cent. of the blood urea nitrogen, with a minimum of 60

per cent. and a maximum of 180 per cent. In this group the percentage of creatinin averaged somewhat less, from 67.31 per cent., with a minimum of 30 per cent. and a maximum of 91 per cent. of the blood creatinin. The averages for the corresponding group of thoracic transudates, in cases with normal blood metabolites, was quite similar. In this

TABLE 3.—GROUP I. A. ASCITIC AND THORACIC TRANSUDATES WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Carcinomatosis	0.096	0.102	106.25	.....	.....	.....	1.844	1.600	86.00
2	Ascitic	Carcinomatosis	0.104	0.080	76.90	17.85	14.00	78.00	1.416	0.435	30.00
3	Ascitic	Hepatic cirrhosis	.....	.....	.....	.....	.....	.....	1.700	1.250	73.00
4	Ascitic	Hepatic cirrhosis	0.086	0.071	82.50	14.00	9.10	65.00	1.790	1.610	91.00
5	Ascitic	Hepatic cirrhosis	0.093	0.095	102.00	17.85	14.35	79.00	1.960	1.540	78.00
6	Ascitic	Hepatic cirrhosis	0.114	0.105	92.00	10.85	12.60	116.00	1.820	1.000	54.92
7	Ascitic	Hepatic cirrhosis	0.109	0.165	60.00	28.70	28.00	97.50	2.000	1.170	58.50
8	Ascitic	Hepatic cirrhosis	0.123	0.071	51.00	11.55	20.90	180.00	1.807	1.110	61.00
9	Ascitic	Gastric carcinoma	0.100	0.096	96.00	11.80	11.90	100.00	1.860	1.570	84.00
10	Ascitic	Hydrocele	0.102	0.087	85.00	5.25	3.15	60.00	2.360	1.500	63.50
11	Ascitic	Hepatic cirrhosis	0.083	0.093	112.00	9.10	7.14	78.40	1.180	1.400	77.70
12	Ascitic	Hepatic cirrhosis	0.081	0.088	108.00	8.65	8.05	92.80	1.280	1.300	81.00
13	Ascitic	Chronic nephritis	0.100	0.096	96.00	23.00	23.10	100.00	2.250	1.760	78.20
Av.	Ascitic	.....	0.099	0.096	96.47	14.43	13.84	95.90	1.958	1.318	67.31
1	Thoracic	Chronic nephritis	0.133	0.138	103.76	18.88	21.68	114.30	2.770	2.380	85.90
2	Thoracic	Aneurysm of arch	0.098	0.079	80.60	14.00	13.65	97.50	2.110	1.310	62.56
3	Thoracic	Chronic nephritis	0.100	0.086	86.00	23.00	.....	.....	2.250	1.730	76.80
4	Thoracic	Chronic nephritis	0.100	0.088	88.00	23.00	23.80	100.30	2.250	1.790	79.40
5	Thoracic	Myocardic degeneration	0.112	0.091	81.20	15.05	8.40	55.70	1.630	1.110	66.60
6	Thoracic	Myocardic degeneration	0.094	0.082	87.20	14.00	5.25	37.50	1.760	1.320	75.00
7	Thoracic	Chronic nephritis	0.133	0.127	95.48	18.88	18.60	98.64	2.770	2.307	84.00
Av.	Thoracic	.....	0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
Average.....			0.104	0.098	94.23	16.27	13.30	89.30	2.089	1.512	72.38

group the average sugar content of the fluid was 90 per cent., with a minimum of 80.6 per cent. and a maximum of 103.76 per cent. The urea nitrogen averaged 84.09 per cent., with a minimum of 37.5 per cent. and a maximum of 114.3 per cent. of the blood urea nitrogen. The creatinin averaged 76.89 per cent. with a minimum of 62.56 per cent. and a maximum of 85.9 per cent. (Table 3).

The corresponding exudates showed slightly lower percentages than the transudates. The sugar content of the ascitic transudates with normal blood metabolites averaged 75.55 per cent., with a minimum of 59 per cent. and a maximum of 98 per cent. The urea nitrogen averaged 70.02 per cent., with a minimum of 41 per cent. and a maximum of 113 per cent. The creatinin averaged 48.8 per cent., with a minimum of 35 per cent. and a maximum of 72 per cent. In the corresponding group of thoracic exudates, the sugar content averaged 79.32 per cent., with a minimum of 0 (case of acute empyema), and a maximum of 106.9 per cent. The urea nitrogen in this group averaged

TABLE 4.—Group I. B. Ascitic and Thoracic Exudates with Normal Blood Metabolite Concentrations

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Tuberculous peritonitis	0.114	0.075	65.00	12.78	5.33	41.00	2.000	0.900	45.00
2	Ascitic	Tuberculous peritonitis	0.126	0.075	59.00	29.65	14.89	50.00	2.550	1.200	47.00
3	Ascitic	Polyserositis	0.102	0.084	82.00	23.55	22.42	95.00	2.850	1.000	35.00
4	Ascitic	Acute peritonitis	0.108	0.106	98.00	8.65	9.80	113.00	2.080	1.500	72.00
Av.	Ascitic	.....	0.113	0.085	75.55	18.66	13.11	70.02	2.370	1.150	48.80
1	Thoracic	Empyema	0.088	0.000	00.00	.....	.....	.....	2.000	1.400	70.00
2	Thoracic	Tuberculous pleurisy	0.083	0.087	104.80	24.05	22.05	91.69	1.740	1.730	99.90
3	Thoracic	Tuberculous pleurisy	0.098	0.102	104.10	28.70	21.30	73.17	2.500	2.050	82.00
4	Thoracic	Tuberculous pleurisy	0.095	0.097	102.20	12.60	13.60	104.00	2.110	1.780	84.32
5	Thoracic	Tuberculous pleurisy	0.101	0.108	106.90	22.20	18.20	81.90	1.880	1.760	93.61
6	Thoracic	Empyema, lues	0.160	0.096	60.00	13.30	10.15	76.31	2.330	1.600	69.53
7	Pericardial	Acute pericarditis	0.100	0.086	86.00	14.00	12.46	89.00	2.000	1.410	70.50
Av.	Thoracic	.....	0.103	0.082	79.32	19.14	16.29	86.01	2.066	1.621	78.41
Average			0.108	0.083	77.93	18.90	14.70	78.01	2.212	1.385	62.16

86.01 per cent., with a minimum of 73.17 per cent. and a maximum of 100 per cent. The creatinin figures averaged 78.41 per cent., with a minimum of 69.53 per cent. and a maximum of 99.9 per cent. (Table 4).

The cerebrospinal fluids in cases with normal blood metabolite concentration show consistently lower percentages of metabolites. The figures for the normal and pathologic fluids yield remarkably similar figures. The spinal fluid sugars averaged 60.21 per cent., with a minimum of 40.1 per cent. and a maximum of 89.6 per cent. In the same group the spinal fluid urea nitrogen averaged 66.5 per cent., with a

minimum of 39.9 per cent. and a maximum of 140 per cent. The creatinin averaged 59.8 per cent., with a minimum of 22.03 per cent. and a maximum of 90 per cent. (Table 5).

Although the bloods from the group of cases with increased metabolite concentration show a decided rise above the normal blood

TABLE 5.—GROUP III. NORMAL AND PATHOLOGICAL CEREBROSPINAL FLUIDS WITH NORMAL BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Normal	Cholecystitis	0.102	0.055	53.93	12.60	4.65	39.90	1.148	0.253	22.03
2	Normal	Neurasthenia	0.092	0.063	68.48	13.65	8.60	63.00	0.968	0.343	35.33
3	Normal	Gastric carcinoma	0.080	0.037	46.45	.....	.....	.....	1.800	1.300	73.33
4	Normal	Cirrhosis	0.074	0.055	74.32	.....	.....	.....	2.340	1.360	58.12
5	Normal	Hysteria	0.087	0.052	60.00	.....	.....	.....	1.807	1.310	71.80
6	Normal	Dementia praecox	0.097	0.064	66.00	9.80	8.30	84.50	1.720	1.210	70.30
7	Normal	Normal	0.073	.....	.....	10.85	7.00	64.00	2.000	1.200	60.00
Av.	Normal	.....	0.086	0.054	61.58	11.73	7.16	61.00	1.683	0.997	59.20
1	Path.	Neurosyphilis	0.102	0.041	40.10	18.80	9.80	51.60	1.820	1.200	66.00
2	Path.	General paresis	0.166	0.084	50.60	20.30	9.80	48.27	2.000	1.470	73.50
3	Path.	Tabes dorsalis	0.102	0.050	49.00	.....	.....	.....	0.960	0.680	71.66
4	Path.	Enceph. letharg.	0.125	0.074	59.30	.....	.....	.....	1.416	0.343	24.18
5	Path.	General paresis	0.093	0.050	53.76	11.20	15.70	140.00	1.500	0.340	22.80
6	Path.	General paresis	0.105	0.060	57.14	13.48	7.64	56.60	1.000	0.900	90.00
7	Path.	Tabes dorsalis	0.155	0.139	89.60	19.90	16.80	84.42	1.870	1.310	70.00
8	Path.	Tabes dorsalis	0.097	0.055	56.50	7.77	4.90	63.69	1.780	1.090	59.90
Av.	Path.	.....	0.118	0.069	58.90	15.24	10.77	70.60	1.543	0.935	60.60
Average			0.102	0.063	60.21	13.48	8.96	66.50	1.613	0.965	59.80

TABLE 6.—GROUP II. ASCITIC AND THORACIC TRANSUDATES WITH INCREASED BLOOD METABOLITE CONCENTRATIONS

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Ascitic	Chronic nephritis	0.325	0.259	76.00	84.20	96.00	114.00	2.88	2.45	85.00
1	Thoracic	Chronic nephritis	0.107	0.152	111.80	.....	.....	.....	4.22	3.98	94.31
2	Thoracic	Chronic nephritis	0.225	0.308	91.69	84.20	93.00	110.45	2.88	2.61	90.62
3	Thoracic	Chronic nephritis	0.325	0.294	90.46	84.20	97.00	115.20	2.88	2.50	86.11
Av.	Thoracic	.....	0.252	0.251	99.70	84.20	95.00	112.00	3.33	3.03	91.10
Average			0.288	0.255	88.30	84.20	95.50	113.00	3.10	2.74	88.20

values, the relative concentration of the metabolites in the fluids remains much the same as in the cases without retention. This indicates a corresponding increase in the metabolite content of the fluids. The average sugar content of the effusions with increased blood metabolites was 88.3 per cent. as compared with 90 per cent. in the

cases without retention. The urea nitrogen averaged 113 per cent., as compared with 89.3 per cent. and the creatinin 88.2 per cent., as compared with 76.89 per cent. in the normal group (Table 6).

Similarly, where the blood metabolites are increased, the cerebrospinal fluids show a corresponding increase, so that the percentage concentration remains approximately the same as in the group without retention. This is exclusive of a case of acute meningitis in which no spinal fluid sugar was present. In this group the average sugar content was 27.7 per cent., with a minimum of 0 and a maximum of 98.7 per cent. The urea nitrogen averaged 49.8 per cent., with a minimum of 45.9 per cent. and a maximum of 107.9 per cent. The creatinin 73.57 per cent., with a minimum of 39.74 per cent. and a maximum of 102.6 per cent. (Table 7).

The most significant point shown by the data summarized in Table 8 is the relative uniformity of the findings in the various groups. In

TABLE 7.—Group IV. Normal and Pathological Cerebrospinal Fluids with Increased Blood Metabolite Concentrations

Case No.	Fluid	Diagnosis	Sugar			Urea Nitrogen			Creatinin		
			Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.	Blood	Fluid	Per Cent.
1	Normal	Hysteria	0.105	0.069	65.71	27.93	12.78	45.90	3.90	1.35	39.74
2	Normal	Nephritis, tabes	0.099	0.046	44.66	28.70	30.80	107.90	2.21	1.64	74.40
3	Normal	Alcoholism	0.112	0.091	80.80	46.80	49.70	106.00			
4	Normal	Uremia	0.165	0.083	98.70	.....	.....	.....	9.74	9.99	102.60
Av.	Normal	.....	0.120	0.072	60.00	50.53	31.09	61.10	5.28	4.26	80.69
1	Path.	Cerebrospinal meningitis, tabes, nephritis	0.140	0.000	00.00	107.00	45.6	42.61	3.0	2.11	70.33
Average.....			0.130	0.036	27.70	78.76	38.34	49.80	4.14	2.073	73.57

general, the concentration of sugar, urea nitrogen and creatinin in the fluids of all the groups tends to approximate 80 per cent. of their respective concentration in the blood. The spinal fluids are consistently lower than the effusions, approximating 60 per cent. of the blood figures. The concentration of creatinin in all the fluids tends to remain relatively lower than the other metabolites in comparison with their respective blood values.

Of special interest is the fact that in Groups II and IV, in which the blood metabolites are increased, the percentage of metabolites in the fluids in relation to the blood is approximately the same as in the cases with normal metabolite levels. This indicates a definite tendency toward equilibrium in the distribution of metabolites between the blood and fluids. This parallelism is well illustrated in Chart I, which shows the findings from a case of chronic nephritis, with ascites and bilateral hydrothorax. On admission the patient's blood urea nitrogen was

87.2 mg. per hundred cubic centimeters, with urea nitrogen values for the pleural effusions and ascitic fluid of 93, 97 and 96 mg. per hundred cubic centimeters, respectively. Five weeks later, under dietary treatment and rest in bed, the blood urea nitrogen had dropped to 23 mg., the right pleural effusion to 23.8 mg., the left pleural effusion to 23.8 mg., and the ascitic fluid to 23.1 mg. per hundred cubic centimeters, respectively. In another five weeks the blood urea had fallen to 18.8 mg., with corresponding drops to 21.68, 18.60 and 19 mg. per hundred cubic centimeters, respectively, in the three fluids. The creatinin and sugar values show equally consistent decreases in the blood and three fluids. Although at the time of the first estimations five liters of fluid were removed, and five and a half liters at the time

TABLE 8.—SUMMARY OF RESULTS. AVERAGE RELATIVE CONCENTRATION OF METABOLITES IN THE BLOOD AND VARIOUS BODY FLUIDS

Classification of Fluids				Metabolite Determinations								
				Sugar			Urea Nitrogen			Creatinin		
Blood Metabolites	No. Cases	Source	Type	Blood	Fluid	Per Cent.*	Blood	Fluid	Per Cent.*	Blood	Fluid	Per Cent.*
Group I Normal	13	Ascitic	Trans.	0.099	0.096	96.47	14.13	13.84	95.90	1.958	1.378	67.31
	7	Thoracic	Trans.	0.110	0.099	90.00	18.11	15.23	84.09	2.220	1.707	76.89
	4	Ascitic	Exud.	0.113	0.085	75.55	18.86	13.11	70.02	2.370	1.150	48.80
	7	Thoracic	Exud.	0.103	0.082	79.32	19.14	16.29	85.10	2.066	1.621	78.41
Group II Increased	1	Ascitic	Trans.	0.325	0.259	76.00	84.20	96.00	114.00	2.880	2.450	85.00
	3	Thoracic	Trans.	0.252	0.251	99.70	84.20	95.00	112.00	3.326	3.039	91.10
Group III Normal	7	C. S. Fl.	Normal	0.086	0.054	62.79	11.73	7.16	61.00	1.638	0.996	59.20
	8	C. S. Fl.	Path.	0.118	0.069	58.80	15.24	10.77	70.60	1.543	0.935	60.60
Group IV Increased	4	C. S. Fl.	Normal	0.120	0.072	60.00	50.53	31.00	61.10	5.280	4.260	80.69
	1	C. S. Fl.	Path.	0.140	0.000	00.00	107.00	45.60	42.60	3.000	2.110	70.33
Total	55											

Sugar in per cent. urea nitrogen and creatinin in milligrams per 100 c.c.

* Per Cent. $= \frac{\text{Concentration in fluid}}{\text{Concentration in blood}} \times 100.$

of the second determination, the metabolite concentration in all the fluids continued to fall. The reaccumulation of effusions appears to bear no relationship to changes in the retention of these metabolites.

No relation between the metabolite figures in the fluids and the clinical diagnoses was apparent.

DISCUSSION

As previously mentioned, there are two other methods for studying the distribution of metabolites in the body. Postmortem analysis of the urea content of various tissues was first employed by Schoendorf [16] in 1899. In a well fed dog he found that the liver, spleen, pancreas and

16. Schoendorf: Arch. f. d. ges Phys. **74**:307, 1899.

brain contained approximately the same concentration of urea as the blood (from 0.1115 to 0.1228 per cent.), while the heart contained slightly more and the muscle slightly less. Marshall and Davis [17] criticized these findings as being too high for the blood, and probably even less correct for the tissues. They introduced the more accurate urease method of urea estimation, and studied the urea content of normal dogs' tissues, postmortem. They found that the percentage of urea was practically constant throughout the body, except the urinary tract, averaging from 28 to 30 mg. per hundred grams. Similar results were obtained in postmortem analyses of various human organs. By killing dogs soon after the ingestion of urea per os, they were also able to show that it diffused very rapidly into all the tissues, and whether the urea concentration in the body was normal or increased, it was distributed with remarkable uniformity throughout the various tissues. In similar experiments, Foster and Davis [18] found that the amounts of retained nitrogen could not be accounted for by the total nonprotein nitrogen of the total blood of the body. Postmortem analyses of the tissues led them to conclude that more of the nitrogenous metabolites are retained in the tissues than in the blood. Becker [19] studied the total nonprotein nitrogen in nephrectomized dogs. The relatively greatest increase was in the blood, but the absolutely greatest increase was in the muscles. The increase in the other organs was slight in comparison with the musculature. He found a much closer agreement between the urea nitrogen of the tissues and blood than in the total nonprotein nitrogen. Becker also showed that the increase in total nonprotein nitrogen in the various tissues of dead bodies was related to their respective total nitrogen content, with a fairly constant nonprotein nitrogen: total nitrogen ration of 1 : 10. Becker states that postmortem analyses of blood nitrogen are more nearly comparable to postmortem tissue analyses than blood analyses obtained antemortem.

Rosenberg [20] estimated the metabolites in the blood and thigh muscle of nine normal men, eleven chronic nephritics and seven acute nephritics. The blood was taken either just before or immediately after death, and the thigh muscle as soon as possible postmortem. He extracted the musculature with trichloracetic acid, and determined the total rest nitrogen by Kjeldahl's method, urea by the hypobromite

17. Marshall and Davis: J. Biol. Chem. **18**:53, 1914.

18. Foster and Davis: Proc. Soc. Exper. Biol. & Med. **8**:33, 1915.

19. Becker: Deutsch. Arch. f. klin. Med. **128**:1, 261, 1918, ibid. **129**:1, 8, ibid. **134**:325, 1920, ibid. **135**:331, 1920. Becker and Strauss: Zentralbl. f. Inn. Med. **42**:345, 1921.

20. Rosenberg: Arch. f. exper. Path. u. Pharmakol. **86**:1, 1920, ibid. **87**:86, 1920, ibid. **87**:153, 1920.

method, creatinin by Folin's method, and indican by the method of Jolles. Rosenberg's average figures for normal blood and muscle are as follows:

	Blood		Muscle	
Rest nitrogen	0.025	per 100 c.c.	0.307	per 100 gm.
Urea nitrogen	0.020	per 100 c.c.	0.232	per 100 gm.
Creatinin	0.0015	per 100 c.c.	0.00355	per 100 gm.

In two cases in which the normal musculature of the thigh was obtained at amputations for disease below the knee, and analyzed immediately, the results were virtually identical with those for muscle analyzed postmortem. Although the hypobromite method which he used gives figures for urea nitrogen approximately twice those obtained by the urease method,[4] it is difficult to reconcile Rosenberg's figures of 232 mg. per 100 gm. for the urea content of normal musculature with Marshall and Davis of from 28 to 30 mg. per 100 gm. On the other hand, the proportion of rest nitrogen made up of urea nitrogen in Rosenberg's figures is about that generally accepted as normal. His figures for normal blood metabolites, also, are within the generally accepted limits. Rosenberg found similiar values for the musculature of rabbits.

From a comparison of the blood chemistry and the postmortem muscle analyses Rosenberg concludes:

> In uremia the muscle rest nitrogen begins to increase when the blood level rises above 170 mg. per hundred cubic centimeters. There is no difference between acute and chronic cases. . . . It is probable that there is a reciprocal relation between the blood and tissues and not, as von Monakow [20] thought, that the tissues fill with metabolites and then overflow into the blood. . . . In the muscles of chronic nephritics it is found not only that the urea nitrogen increases to a relatively higher degree than the other nonprotein nitrogenous metabolites, but that these may even diminish, possibly through the conversion of amino-acids into urea. . . . The muscle urea shows an increase when the blood urea rises above 150 mg. per hundred cubic centimeters. . . . In all cases showing increased muscle urea the absolute increase of urea in the blood was considerably less than in the musculature. . . . The muscle creatinin increase was inconstant, and occurred only with severe creatininemia.

According to Rosenberg, then, normal muscle values for the rest nitrogen and urea are over ten times their concentration in the blood, and are not increased until the blood level rises above approximately two thirds of the normal muscle concentration. Retention of urea in the musculature occurs earlier than the other metabolites and its disproportionate increase in the muscles is probably due to the conversion of other nonprotein metabolites into urea.

Weiss and Vaughn [21] recently reported a case of severe nephritis in which the blood urea twelve hours before death was 304 mg., and the nonprotein nitrogen 401 mg. per hundred cubic centimeters. Post-

21. Weiss and Vaughn: J. Lab. & Clin. Med. **7**:229, 1921.

mortem, the pericardial fluid contained 374 mg. of urea nitrogen, the muscle 352 mg., and the liver 335 mg. per hundred grams, respectively. Their technic is not given, but the results show a close approximation of the urea content of the blood, fluid and tissues. Andresen [22] reports an equal distribution of urea, between the blood, organs and secretions, with the exception of tears and sweat, where a value three times that of the blood was found.

With the exception of Rosenberg, all of these investigators appear in fair agreement in regard to the uniform distribution of urea. He diverges considerably in regard to the urea value for normal musculature, but agrees with the others that the urea accounts for most of the nonprotein nitrogen retention in the body.

The distribution of ingested nitrogen was first studied by Soetbeer [23] in 1909. Four and one-half hours after a heavy meal of meat he found the total nitrogen in a dog's blood had increased 132 per cent., in the liver 41 per cent., and in the brain and muscles only 5 or 6 per cent. Seventy-two hours after nephrectomy, the total nitrogen in a dog's blood had increased 873 per cent., in the liver 144 per cent., in the brain 40 per cent., and in the muscles only 35 per cent. This would indicate a heaping up of the retained nitrogen in the blood before its accumulation in the tissues.

Von Monakow [24] showed that after a single ingestion of 20 gm. urea per os, in normal men, the blood urea rose in fifteen minutes and reached its peak in two hours, remaining slightly increased at twenty-four hours and returning to normal on the second day. If one day after the first ingestion, a second 20 gm. was given, the blood urea level still returned to normal within two days. In other words, it was impossible to raise the blood level by repeated small doses of urea per os. Von Monakow assumes that most of the ingested urea passes into the tissues.

Lichtwitz [25] repeated these experiments, controlling them with simultaneous estimations of nitrogen elimination in the urine. After the ingestion of 20 gm. urea per os, he found widely varying percentages of the retained urea in the blood. He concludes that the rest nitrogen is very unequally divided between the blood and other organs, and that it need not be increased in the blood, although the amount of nitrogen eliminated indicates a definite nitrogen retention.

Nonnenbruch [26] has recently repeated similar experiments on urea ingestion, retention, and elimination. He finds that the variations in

22. Andresen: Biochem. Ztschr. **116**:266, 1921.
23. Soetbeer: Verhandl. 26 Cong. f. inn. Med., 1909.
24. Von Monakow: Deutsch. Arch. f. klin. Med. **115**:47, 224, 1914; ibid. **116**:1, 1914.
25. Lichtwitz: Klinische Chemie, 1918.
26. Nonnenbruch: Arch. f. exper. Path. u. Pharmakol. **89**:200, 1921.

blood urea nitrogen following the oral ingestion of 20 gm. urea, do not parallel its elimination. For the most part the nonprotein nitrogen of the blood does not increase sufficiently to account for the urea ingested and falls much more rapidly than it is eliminated in the urine. In some cases, blood urea nitrogen was still increased after the ingested urea had all passed out through the kidneys. Several cases showed two peaks and two troughs in the blood rest nitrogen curves. On the basis of these findings, Nonnenbruch concludes that there is a marked difference of distribution between the blood and other tissues; that a normal blood rest nitrogen does not indicate the absence of nitrogen retention, nor, on the contrary, does an increased blood nitrogen indicate nitrogen retention in the tissues. He thinks that immediately after its ingestion urea is carried to the tissues and afterward returned to the kidneys for elimination.

SUMMARY

Although the studies with ingested urea indicate that during the period of its elimination there is no constant parallelism in the concentration of nitrogenous metabolites of the blood and tissues, both the estimation of the body fluid metabolites and the comparison of metabolites in the blood and tissues, strongly suggest a tendency to equilibrium throughout the organism. This does not necessarily mean that a normal concentration of metabolites in the tissues approximates that in the blood, but that the metabolites are distributed between them in a fairly constant proportion, and that an increase in one is paralleled by a proportionate increase in the other. No account, of course, is taken here of any but the simple metabolites; available sugar in the form of glycogen, or available rest nitrogen, urea nitrogen, creatinin or uric acid in more complex chemical forms, are incalculable factors. The distribution of creatinin and sugar throughout the body is for the most part unknown.

The distribution of metabolites between the blood and all the body fluids is fairly consistent. For clinical purposes, it appears justifiable to deduce from the concentration of metabolites in the blood, an approximately proportional concentration throughout the whole body. Nevertheless, until the distribution of metabolites for all the tissues is quantitatively determined, it will remain impossible to deduce accurately from the blood chemistry alone the degree of retention in the whole body.

CONCLUSIONS

1. In cases in which the blood metabolite level was not increased above normal, the concentration of sugar in serous effusions averaged 83.42 per cent. of the sugar concentration in the blood. The urea nitrogen averaged 80.08 per cent., and the creatinin 67.28 per cent.

2. No characteristic difference in the metabolite concentration of exudates and transudates was observed.

3. In cases in which the blood metabolite level was normal, the average concentration of sugar in the spinal fluid was 44.24 per cent. of the blood sugar. Urea nitrogen averaged 58.15 per cent., and creatinin 68.3 per cent.

4. Except for the absence of sugar in acute meningitis, no difference was present between normal and pathologic spinal fluids.

5. In cases in which the blood metabolite level was increased, the metabolite concentration in the fluids varied pari passu with the changes in the blood.

Thanks are due to Drs. S. Marx White and George Fahr for their kind permission to study cases in the University Hospital, and to Dr. Henry L. Ulrich for the use of several private cases, and cases in the Minneapolis General Hospital.

QUINIDIN IN AURICULAR FIBRILLATION

WITH SOME OBSERVATIONS ON ITS USE IN COMBINATION WITH DIGITALIS *

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One of the most spectacular medical discoveries of recent years is the effect which alkaloids of cinchona have on certain hearts presenting the phenomenon of auricular fibrillation.

Quinin has been used for many years as a heart sedative, but its use specifically in auricular fibrillation dates from a report of two cases published in 1914 by Wenckebach [1] in which its administration resulted in the restitution of sinus rhythm.

As a result of his studies of the effect of various alkaloids of cinchona on patients suffering from auricular fibrillation, Frey [2] came to the conclusion that quinidin was the least toxic and the most potent of these derivations, and because of its better solubility he advised the use of the sulphate instead of the pure alkaloid.

Since Frey's paper in 1918 there have appeared in the literature the reports of more than 300 cases of auricular fibrillation treated with quinidin. In about one half of these its administration has been followed by a resumption of normal rhythm which has persisted for periods varying from a few hours to several months.

We have as yet little accurate knowledge of the exact manner in which quinidin accomplishes its results, its optimum dose, the intervals at which it is best administered, its rate of elimination and its dangers. We know little of the type of case in which the normal rhythm is likely to be restored and the value of the resumption of control by the normal pacemaker is still open to discussion. The advantages and disadvantages of combining the administration of quinidin with other drugs has been studied but little.

It is only by accumulating considerable data that many of these questions can be solved, and it has, therefore, been considered worth while to place on record the clinical observations which we have secured up to the present time, notwithstanding their limited number and rather fragmentary character.

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* From the Medical Service of the Presbyterian Hospital.

* Read before the Association of American Physicians, Washington, D. C., May 3, 1922.

1. Wenkebach: Die unregelmässige Hertztätigkeit und ihre klinische Bedeutung, Leipzig, 1914.

2. Frey: Berl. klin. Wchnschr. **55**:417, 451, 1918.

This report is based on a rather careful study of fifteen persistent and two paroxysmal cases of auricular fibrillation. These were unselected cases, such as one meets in the medical service of a large general hospital. The patients were observed carefully, were subjected to the usual routine physical and laboratory examinations of a well ordered medical service, and were studied by means of electrocardiographic records taken at frequent intervals.

The drug employed in all the studies has been the sulphate of quinidin, administered in capsules, each containing 0.2 gm. Our routine has been to give two preliminary doses of 0.2 gm. each allowing twenty-

TABLE 1.—CASES IN WHICH THE ADMINISTRATION OF QUINIDIN WAS FOLLOWED BY SINUS RHYTHM

Case No.	Sex	Age	Clinical Diagnosis	Duration of Fibrillation Before Quinidin	Quinidin, Gm.	Duration of Sinus Rhythm
1	M	31	Chronic valvular disease, mitral stenosis, mitral insufficiency, cardiac insufficiency, repeated attacks of rheumatism	2 weeks	2.8 in 3 days 2.4 in 2 days	10 weeks 2 days
3	M	72	General arteriosclerosis, cardiac hypertrophy, hypertension, chronic nephritis	?	1.4 in 2 days	12 days
5	F	43	Hyperthyroidism, exophthalmic goiter, ligation of superior thyroid artery	3 years	1.4 in 2 days 1.8 in 2 days 3.6 in 4 days	24 hours 48 hours 0
9	F	68	Chronic nephritis, cardiac hypertrophy, hypertension	1 year	1.4 in 2 days 0.4 in 5 hrs.	7 months 5 mos. still continues
15	F	24	Chronic valvular disease, mitral stenosis, mitral insufficiency, cardiac hypertrophy, cardiac insufficiency, congenital syphilis	18 weeks	1.1 in 40 hrs. 0.6 in 24 hrs. 1.0 in 24 hrs.	6 weeks 6 weeks ?
16	F	44	Exophthalmic goiter, ligation of superior thyroid artery, paroxysmal fibrillation	1 year	2.6 in 2 days 1.2 in 1 day 2.0 in 2 days	48 hours 72 hours 40 hours
17	M	68	Chronic myocarditis, cardiac insufficiency, paroxysmal fibrillation	5 years	0.4 daily for 12 months	1 year still continues

four hours for evidence of individual susceptibility to develop. After this, 0.4 gm. was given after eating three times a day over periods of variable length. As soon as a sinus rhythm had been reestablished the drug was immediately discontinued. Noteworthy departures from this routine will be mentioned in connection with the description of special cases.

Of the fifteen patients showing persistent auricular fibrillation, five recovered a normal rhythm after the administration of quinidin; in all fibrillation recurred after a longer or shorter period (Table 3); in four of these quinidin was given again and in each instance the normal pacemaker assumed control of the rhythm. One of these patients still

maintains a normal rhythm after an interval of five months; in the other three cases, a third period of quinidin was effective in one and ineffective in the remaining two cases.

Flutter, as a transitional mechanism preceding a sinus rhythm, was recorded in two cases. In three other cases the administration of quinidin was followed by flutter (one case) and impure flutter (two cases) but in these cases the sinus never regained its control as a pacemaker.

In both paroxysmal cases, sinus rhythm promptly followed small doses of quinidin. In Case 16 of our series the periods of sinus rhythm were so brief and so similar to those of the control period during which no quinidin was given that our observations appeared to be of little or no value. The results obtained in Case 17 were more striking and will be referred to later in more detail.

In our experience, if quinidin was effective in producing sinus rhythm, this occurred within a few hours, or, at least, not longer than sixty hours after beginning the use of the drug. In one case sinus rhythm was restored in five hours after the administration of 0.4 gm. To none of the cases in which it was effective was more than 3 gm given. In the cases which did not resume a normal rhythm, quinidin, 1.2 gm. a day, was continued from one to three weeks, but the prolonged administration seemed to have little or no effect. One patient (Case 1) who on two occasions responded to small doses of quinidin and in a third period failed to respond, was given, in a fourth period, 0.6 gm. daily for forty consecutive days with no apparent change in his rhythm or condition.

SELECTION OF CASES

We are able to add very little new information as to the type of case that is likely to be affected favorably by quinidin. In Table 1 are grouped the cases in which the administration of quinidin was followed by a sinus rhythm; in Table 2 the cases in which fibrillation persisted. A comparison of the sexes, ages and length of duration of fibrillation in these cases affords no explanation of the type of case in which quinidin exerts its peculiar influence. Nor does the clinical diagnosis help in solving this question. Cases of chronic valvular disease, mitral disease, general arteriosclerosis, chronic nephritis, chronic myocarditis, hyperthyroidism and hypertension can be found in both groups.

There is one feature, however, to which we would like to call attention which may possibly be of value in selecting the cases in which the administration of quinidin may be followed by the restoration of sinus rhythm. In reviewing our electrocardiographic curves, we have been impressed by the fact that those patients who in their control curves (i. e. those taken in the period before quinidin was given)

showed relatively large auricular waves or in which the coarse waves predominated over the fine waves, were more likely to regain a normal rhythm than those patients whose control curves showed only fine auricular oscillations.

Of the control curves of fifteen cases of persistent fibrillation, nine presented very coarse waves or a mixture of fine and coarse waves in which the latter predominated. Of these, four reverted to normal rhythm. Six of these cases showed only the finer auricular waves and of these only one returned to a sinus pacemaker. A number of patients showing only fine oscillations had received digitalis over considerable periods, and this is an important point to be considered as will be seen when we discuss the influence of digitalis. In this connection, it is of interest to recall that cases of auricular flutter, in which auricular waves are, as a rule, relatively large, are more likely to recover a sinus rhythm spontaneously than cases of auricular fibrillation.

TABLE 2.—CASES IN WHICH THE ADMINISTRATION OF QUINIDIN WAS NOT FOLLOWED BY SINUS RHYTHM

Case No.	Sex	Age	Clinical Diagnosis	Duration of Fibrillation Before Quinidin
2	M	61	Multiple serositis, chronic myocarditis	5 years
4	F	30	Exophthalmic goiter, acute rheumatic fever, cardiac hypertrophy	7 weeks
6	F	37	Chronic valvular disease, mitral stenosis and insufficiency, rheumatic, cardiac insufficiency	2 weeks
7	F	42	Chronic valvular disease, mitral stenosis, aortic insufficiency, cardiac hypertrophy, cardiac insufficiency	Over 2 years
8	M	60	Chronic myocarditis, cardiac hypertrophy, cardiac insufficiency	? years
10	F	60	Chronic valvular disease, mitral stenosis and insufficiency, general arteriosclerosis, cardiac hypertrophy, cardiac insufficiency	Unknown
11	F	18	Chronic valvular disease, mitral stenosis and insufficiency, aortic stenosis, cardiac hypertrophy, cardiac insufficiency, rheumatic	7 days
12	M	61	General arteriosclerosis, chronic myocarditis, cardiac insufficiency	Unknown
13	F	42	Chronic valvular disease, mitral stenosis and insufficiency, cardiac hypertrophy, rheumatic, general arteriosclerosis	Unknown
14	F	16	Chronic valvular disease, mitral insufficiency, cardiac hypertrophy, adherent pericardium, cardiac insufficiency	7 months

QUINIDIN IN COMBINATION WITH DIGITALIS

A number of those reporting[3] the effects of the administration of quinidin have pointed out that it may be associated with disagreeable symptoms and dangerous or even fatal results. Sir James Mackenzie

3. Eyster and Fahr: Arch. Int. Med. **29**:59 (Jan.) 1922. Hewlett and Sweeney: J. A. M. A. **77**:1793 (Dec. 3) 1921. Mackenzie, J.: Brit. M. J. **2**: 576, 1921. Orr, J.: Brit. M. J. **2**:576, 1921. Benjamin and von Kapf: Deutsch. med. Wchnschr. **42**:10, 1921.

has particularly emphasized the possibility that the sudden coordinated contraction of the auricles may tend to dislodge emboli from intra-auricular thrombi.

Levy has noted the not infrequent occurrence of ventricular tachycardia, and suggests that a persistent use of quinidin in such cases might lead to ventricular fibrillation with its obvious hazard.

It is not surprising that the administration of a drug so dramatic in its effects should at times be attended with dangers, and in the present state of our knowledge it should be used only with great caution and under the closest supervision. None of our patients at any time presented alarming symptoms. A few had ringing in the ears, headache, nausea, vomiting, palpitation and increase in heart rate but these were very temporary and usually disappeared a short time after the drug was discontinued.

In two instances which did not ultimately return to a sinus rhythm numerous ventricular extrasystoles were observed, but these were never so frequent as to suggest the approach of a ventricular tachycardia. One patient after recovering a sinus rhythm exhibited occasional auricular premature contractions.

It was our impression that the greatest discomfort of which our patients complained was due to the palpitation and tachycardia. At the beginning of our work, in order to simplify our experiment as much as possible, we gave quinidin only to those patients who had never received digitalis or we withheld it for two or three weeks until we were sure that the heart was free from recent digitalis influences. This, of course, was the cause of much tachycardia and consequent discomfort. It was thought therefore, that it might be of some practical clinical value to compare in individual cases the result of the administration of quinidin alone with the result in subjects who had also been thoroughly digitalized.

The results of our observations have been collected in Table 3. The cases are presented in the order in which they were studied, the "periods" represent successive intervals in which patients were observed, the time intervening between the periods varying greatly. For example: Case 1 (rheumatic mitral disease) was first under observation in the hospital for about six weeks. The patient was discharged after sinus rhythm had persisted for four weeks. Six weeks later he began to fibrillate, and on his second admission to the hospital he was found to have been digitalized thoroughly. Without waiting for digitalis effects to wear off, he was given quinidin, which was promptly followed by a change to sinus rhythm which, however, lasted only two days. Quinidin was again administered but this time without interrupting fibrillation. In contrast, Case 5, a subject of hyperthyroidism with a metabolism rate of 56 above the normal, received quinidin in successive

periods separated by intervals of only two or three days. The first and second periods resulted in a resumption of control by the normal pacemaker; after this quinidin failed in abolishing fibrillation.

The use of alkaloids of cinchona in combination with digitalis has been opposed on the ground that their pharmacologic activities are antagonistic. Stokvis,[4] experimenting on the frog's heart found that a combination of quinin and digitalis destroyed the depressing action of quinin and modified the excitation due to digitalis. Pezzi and Clerc [5] state that in dogs to which quinin had been given, the subsequent administration of large doses of digitalin produced no toxic symptoms.

Schott [6] has pointed out that in experimental animals quinidin, like digitalis, may produce heart block.

TABLE 3.—Quinidin and Digitalis

Case No.	First Period			Second Period			Third Period		
	Drugs	Effect	Duration	Drugs	Effect	Duration	Drugs	Effect	Duration
1	Q	Sinus	10 wks.	Q + D	Sinus	2 days	Q + D	0	
2	Q	0	.....	Q + D	V slowing				
3	Q	Sinus	12 days						
4	Q	A slowing	.....	Q + D	V slowing A faster				
5	Q	Sinus	24 hrs.	Q	Sinus	48 hrs.	Q	0	
6	Q	A slowing	.....	D	V slowing				
7	Q	A slowing	.....	D	V slowing A faster				
8	Q	0	.....	Q + D	V slowing				
9	D + Q	Sinus	7 mos.	Q	Sinus	5 mos.+?			
10	Q	A slowing							
11	Q	A slowing	.....	Q + D	V slowing				
12	D + Q	V slowing							
13	D + Q	A slowing							
14	D + Q	A slowing							
15	D + Q	Sinus	6 wks.	D + Q	Sinus	6 wks.	D + Q	Sinus	?
16*	D + Q	Sinus	48 hrs.	D + Q	Sinus	3 days	D + Q	Sinus	40 hrs
17*	Q	Sinus	1 year						

* Paroxysmal auricular fibrillation.
A = auricular; V = ventricular; Q = quinidin; D = digitalis.

Frey was opposed to the simultaneous use of quinidin and digitalis. Hewlett and Sweeney [3] think that the administration of digitalis may have lessened the chances of the recovery of sinus rhythm in two of their cases.

In several papers [7] published the latter part of 1921, Lewis and his associates, Drury and Illiesco, pointed out that quinidin caused an "invariable and conspicuous reduction in the auricular rate." They obtained this evidence by applying special electrodes to the chest wall

4. Stokvis: Leçons de Pharmacologie **3**:41, 1905.
5. Pezzi and Clerc: Presse méd. **28**:334, 1920.
6. Schott: Deutsch. Arch. f. klin. Med. **124**:208, 1920.
7. Lewis, Drury and Iliesco: Brit. M. J. **2**:514, 1921. Drury and Iliesco: Brit. M. J. **2**:512, 1921. Lewis, Drury, Iliesco and Wedd: Heart **9**:55, 1921.

and were thus able to secure more clearly defined auricular waves in the electrocardiograms than when electrodes were applied to the extremities.

Since these papers were published, we have scrutinized all our electrocardiographic records taken by the usual leads from the extremities. In these the auricular waves are often not prominent enough to make actual measurements of rate, but where these could be made, the administration of quinidin was uniformly found to slow the auricles and make the auricular waves more prominent.

Our curves further show that when digitalis was given, the auricular waves usually became smaller and more rapid; when it was withdrawn, these waves became coarser.

On several occasions we were able to watch in the same patient the effect of the administration of quinidin alone and later the combined effect of quinidin and digitalis. Curves illustrating the effect on the auricular activity are shown in Figures 1 and 2. The effect of giving quinidin in a case of auricular fibrillation without other medication was to make the auricular waves coarser. After a considerable period of quinidin, digitalis was added and its effect was shown not only by a slowing of the ventricular rate but also by a finer and more rapid auricular activity. Subsequently, quinidin was stopped and digitalis continued alone when its unopposed action was made evident by a further ventricular slowing and still smaller auricular waves. This would appear to be further evidence that there is an antagonism between quinidin and digitalis.

In Case 1 a delayed conduction and in Case 3 a partial block was observed during sinus rhythm, in neither instance could the effect be ascribed to digitalis. Case 15 also showed a delay in the conduction period but this patient was under the influence of both digitalis and quinidin.

As far as evidence based on success or failure in securing sinus rhythm goes, we have no definite proof that quinidin and digitalis are antagonistic.

An analysis of the fifteen cases of persistent fibrillation recorded in Table 3 shows that ten received in the first period quinidin only. In three of these, sinus rhythm was promptly secured. There were seven failures. Five patients received in the first period both digitalis and quinidin. Of these, two recovered a normal rhythm.

While the patients listed in Table 3 as receiving in the "first period" quinidin only were those who had taken no digitalis for two or three weeks preceding the period of observation and so were presumably free from its influence, it seems to us important to take into consideration the fact that a number of them had been digitalized more or less completely on earlier occasions. It was not possible to obtain sufficiently

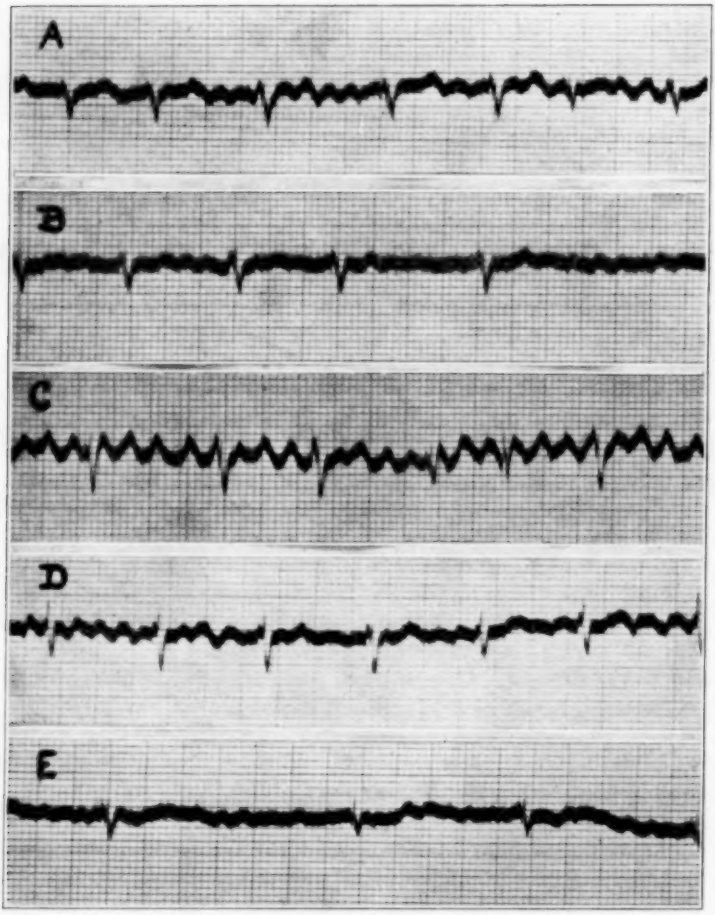

Fig. 1.—Case 4. Lead III. A. April 5. Fibrillation, ff waves rather coarse. No drugs. B. April 18. Fibrillation, ff waves fine. Digitalis only. C. May 24. Flutter, after quindin, 0.2 gm. No digitalis for three weeks. D. June 2. Fibrillation, ff waves medium size. Taking quinidin and digitalis. E. June 13. Fibrillation, ff waves very small. Digitalis only.

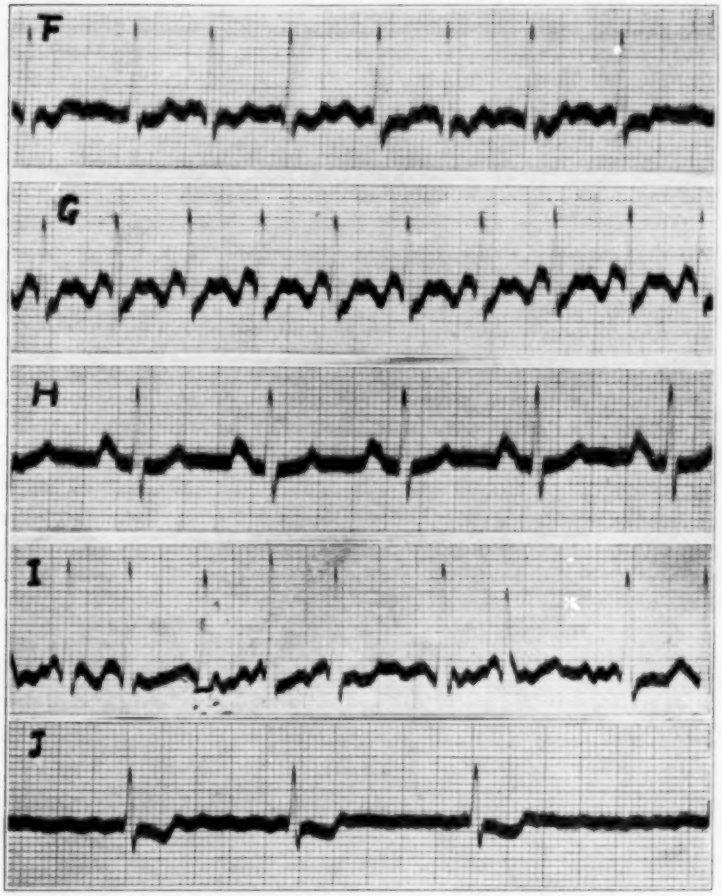

Fig. 2.—Case 1. Lead II. F. May 11. Fibrillation. No drugs. G. May 14. Flutter after quinidin, 2.4 gm. H. May 15. Sinus rhythm after quinidin, 2.8 gm. I. July 28. Fibrillation. No drugs for ten weeks. J. September 15. Fibrillation. Full digitalization, ff waves very small.

reliable statements as regards this feature from many of these patients, hence we have not recorded our incomplete data on this point. The effect of digitalis in diminishing the size of the auricular waves, and the experimental evidence that it can produce fibrillation, suggest that digitalis may have an influence in fixing a condition of fibrillation, and that a heart once digitalized may even after a very long period resist a return to sinus rhythm even though the more obvious influences of digitalis have disappeared.

A brief discussion of the comparative effect in individual cases of the administration of quinidin alone and of quinidin combined with digitalis affords some points of interest.

We may dismiss all those cases (Table 2) in which a sinus rhythm was not secured by stating that, in general, the effect of quinidin was to slow the auricular rate and accelerate the ventricular rate, while digitalis neutralized these effects, increasing the auricular rate and slowing the ventricular rate.

In several of the cases (Table 3) no comparative tests were made. Case 5 responded to quinidin on two occasions and failed to respond in the third. Case 15 was receiving digitalis through the whole period of observation. On three occasions the patient was given quinidin and this was followed by sinus rhythm each time. She has disappeared and we have been unable to report subsequent events. In this instance it does not appear that the digitalis seriously opposed the action of the quinidin, yet it is quite possible that without digitalis her periods of sinus rhythm might have been longer.

Case 1 responded promptly to quinidin; the normal pacemaker remained in control for ten weeks. During this period the patient had returned to his home, and when he again began to fibrillate, he was digitalized under the advice of his family physician. At this time he returned to the hospital and was admitted for observation, the administration of quinidin was again promptly followed by sinus rhythm which, however, lasted only forty-eight hours, quinidin was immediately repeated but a sinus rhythm was not secured. It is difficult to say that this was due to the digitalis, but it is suggestive.

Case 9 presents a number of features of interest.

The patient is a woman, aged 68, who has been under constant supervision for more than ten years. She is suffering from chronic nephritis, and for the past five years her systolic blood pressure has ranged from 200 to 230 mm. Hg; diastolic pressure, from 120 to 140 mm. Hg. Her heart is enlarged, and the mitral valve is incompetent. Except for occasional extrasystoles, her heart was regular until January, 1920. At that time she developed auricular fibrillation which terminated in twenty-four hours. Following this she had paroxysms of fibrillation, each lasting from one to three days, at four or five weeks intervals, until May, when the fibrillation became continuous. She was then digitalized effectively and the heart rate was kept between 70 and 80. In May, 1921, after having fibrillated persistently for one year and while still thoroughly under the influence of digitalis, she was given, in the course of two

days, 1.4 gm. quinidin. This was promptly followed by sinus rhythm and all medication was at once discontinued. A sinus rhythm was maintained for seven months until Dec. 9, 1921, when she notified me about 2 a. m. that her heart was again irregular. She was seen a few hours later and the heart was found to be fibrillating with a ventricular rate of 140. Quinidin, two doses of 0.2 gm. each, was given and the normal pacemaker resumed control five hours later. The ventricular rate was 86. The sinus rhythm has continued up to the present time.

In this instance the quinidin was equally effective both when the patient was completely digitalized and when she was taking no digitalis, but it may be noted that a smaller dose of quinidin was effective under the latter condition. At no time has this patient shown signs of cardiac insufficiency, except of a most insignificant degree, but her experiences of relief when the tumultuous action of the heart was replaced by an orderly rhythm left no doubt as to the marked increase in mental peace and subjective comfort induced thereby.

Such clinical evidence as we are able to present fails to demonstrate just how much influence digitalis exerts in opposing the action of quinidin, but, in the main, it accords with the experimental work in animals which indicates an antagonistic action of the two drugs.

PAROXYSMAL FIBRILLATION

Case 17 was of interest in this group.

A man, aged 68, has been under observation for more than four years. Without discoverable cause he has had paroxysmal attacks of fibrillation since 1916. His heart shows a very moderate enlargement and a slight systolic murmur at the apex and occasional extrasystoles when the sinus is in control of the rhythm. The roentgen ray shows an aorta measuring 7 cm. Between the paroxysms he has no signs of cardiac insufficiency, but when the heart fibrillates, he becomes excessively nervous, passes urine of low specific gravity at frequent intervals, and becomes dyspneic on any attempt at exertion. At first the attacks lasted only a few hours and occurred at irregular intervals separated by periods of several months. They had gradually increased in frequency and persisted for a longer time. In June, 1921, his attacks recurred at intervals of a few days and persisted for periods varying from nine to twenty-eight hours. June 23 he was seen a few hours after the onset of a paroxysm and it was decided to try the effect of quinidin. After his second dose of 0.4 gm. he went to sleep and awoke at midnight with a regular heart. He was advised that if his attacks recurred he should take a dose of quinidin at once and if the irregularity continued the drug was to be repeated in two hours.

He was seen next August 16 and gave the following account from carefully written notes.

Date	Attacks Began	Quinidin, Gm.	Note	Duration of Fibrillation
June 23	2:00 p.m.	0.4 (6:00 p.m.) 0.4 (9:00 p.m.)	Awoke at 12 Attack had stopped	10 hours (?)
July 5	8:30 p.m.	0.4 (8:45 p.m.) 0.4 (11:30 p.m.)	Awoke at 1:30 Attack had stopped	5 hours (?)
July 16	2:30 p.m.	0.4 (2:45 p.m.) 0.4 (5:30 p.m.)	Regular at 7:30 p.m.	5 hours
July 18	4:00 p.m.	0.4 (4:00 p.m.)	Regular at 6:00 p.m.	2 hours
Aug. 10	8:30 p.m.	0.4 (8:30 p.m.)	Regular at 9:30 p.m.	1 hour

Since it appeared that quinidin had an influence in shortening the attacks, he was directed to take a daily dose (0.4 gm) as a prophylactic measure and to report the results in two weeks. He was not heard from again until he presented himself in January, 1922. Soon after his visit of August 16 he decided to go to France and he remained there until January, 1922. He reported that he had had no attacks and that he has taken one dose of quinidin each day throughout the whole period. He was advised to discontinue the quinidin but felt so confident of the beneficial effects of the drug and so fearful of a return of his paroxysms that up to the present time (May, 1922) he has, on one pretext or another, put off the day on which this advice is to become effective. He has had no attacks since Aug. 10, 1921. His heart is doing its work efficiently and there are no evidences of cardiac insufficiency.*

This experience suggests that quinidin may, in some instances, be taken over very long periods with no ill effects, and that it may act as a prophylactic measure to ward off these attacks which may be of a most distressing nature.

EFFECT OF THE RESTITUTION OF SINUS RHYTHM

Quite aside from the possible dangers involved in converting a condition of fibrillation into one of sinus rhythm, the question arises as to whether the patient is or is not benefited by substituting a sinus pacemaker for the impulses arising in a defective auricle. A priori, one would say that the resumption of the normal rhythm should be of advantage, and this we believe is true. In those cases in which cardiac insufficiency has been outspoken, the improvement in the general circulation, following the return to control of the normal pacemaker, has not been better or worse, more rapid or shorter than similar cases treated efficiently with digitalis. In this connection it may be recalled that the efficiency of the heart depends almost wholly on the integrity of the ventricular muscle, and if a reasonably slow rate can be secured, it makes very little difference whether the agent is an effective sinus pacemaker or digitalis. However, there is no question that the patient is far more comfortable when the delirious heart activity has been abolished. Patients are quite conscious of the change and dread the recurrence of the sensations produced by the fibrillating heart. I believe the mental attitude consequent on the disappearance of palpitation is a valuable asset. If sinus rhythm persists for any considerable time there is the additional advantage of discontinuing the administration of drugs for long periods.

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* NOTE.—Seen Aug. 1, 1922. No attacks up to this time. Has taken dose of quinidin daily.

SUMMARY

1. Quinidin administered in fifteen cases of auricular fibrillation was followed by sinus rhythm ten times in five cases. In two paroxysmal cases it was followed by sinus rhythm in both instances.

2. Cases exhibiting electrocardiograms with coarse auricular waves appear to be affected more readily by quinidin.

3. There is some experimental and clinical evidence that the action of quinidin and digitalis are antagonistic.

4. Quinidin decreases the auricular rate and augments the ventricular rate. Digitalis increases the auricular rate and slows the ventricular rate.

5. A case of paroxysmal auricular fibrillation is reported in which under the daily administration of quinidin no paroxysms have occurred for nine months.

6. The advantages of the sinus rhythm over that of fibrillation are discussed.

UNUSUAL PAUCITY OF SYMPTOMS IN SOME CASES OF PONTOCEREBELLAR TUMORS. DIAGNOSTIC DIFFICULTIES*

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Neoplasms developing in the pontocerebellar angle are presumably accompanied by manifestations referable to the cerebellum, pons and certain cranial nerves. If the tumor originates in the cerebellum, cerebellar symptoms will appear first. If the tumor originates in the eighth nerve, the most frequently involved among the cranial nerves, vestibular or auditory symptoms will appear first. Besides the eighth, also the seventh, sixth and fifth nerves are affected quite frequently.

In any given case, in which a pontocerebellar involvement is suggestive, a systematic investigation with regard to the encroachment on the above mentioned portions of the central nervous system is usually made and a diagnosis is arrived at without great difficulty. In some cases, however, the stituation is not so easy and only a repeated examination may render assistance. A third group of cases may be so baffling for want of gross or slight symptoms that no opinion can be rendered even after several examinations: in this category of instances the manifestations are so slight or so indefinite that not only the cerebellum or the cerebellopontine area but even an intracranial condition may not be thought of. Fortunately, such cases are rare, but, nevertheless, they do occur. The seven cases described herewith are examples of such an occurrence.

Before giving a description of them, attention is called to the detailed description of symptoms, for which each case was examined.

A carefully carried out examination was made in a systematic manner in each case.

1. The condition of the cerebellum and of its peduncles was determined from the following investigation: (*a*) The gait with regard to staggering toward one or the other side; (*b*) ataxia of the upper or lower extremities with regard to the finger-to-nose test, to overaction, to dysmetria or hypermetria; (*c*) coordination of movements of the lower extremities in the test of placing the heel of one foot on various parts of the other limb; (*d*) diadochokinesia (quick pronation and supination); (*e*) the position of the head with regard to its inclination to one or the other side, also if an abnormal position found whether it is constant or permanent; (*f*) the presence or absence of

* Read at the meeting of the American Neurological Association held in Washington, D. C., May 2-4, 1922.

abnormal voluntary or passive movements by resistance test. According to Holmes and Steward, in a unilateral involvement of the cerebellum while the patient is flexing his arm on the affected side and the examiner opposes this flexion with his hand and then suddenly removes the latter, the movement of the flexion continues and the hand strikes the chest violently. In normal conditions, the arm will continue for a moment flexing at first but will immediately stop and move in the opposite direction. In passive movements, André-Thomas called attention to the following phenomenon in cerebellar diseases: When the arm is raised to a horizontal position and the forearm is given repeated abrupt movements, the arm on the side of the cerebellar lesion will show very little resistance. The movements of flexion followed by movements of return (extension) are both of greater amplitude than on the normal side where resistance is greater and movements are slower. Similarly, when both elbows are held and alternately adducted and abducted, the resistance is less marked on the affected than on the sound side. In the lower extremities, if the thighs are placed at a right angle to the pelvis and the legs are extended but immediately released, the leg on the affected side will show less resistance and its return to the hanging position will be more rapid than that of its fellow on the sound side. The same author observed that when the patient is told to raise his arm (on the affected side) and to let it fall on his head, it will do so like an inert body, namely, it will rebound several times (springlike phenomenon).

(*g*) Special reflex phenomena. When the patient is placed on an elevated seat with his legs hanging, without touching the floor, and the test is made for the patellar tendon reflex, the normal knee jerk will consist of a sudden extension of the leg and slow return to the position of rest. On the diseased side, if the reflex is present, the movement of extension is of a somewhat greater amplitude and is followed by a series of flexion and extension movements (pendulous type). The same form of reflex is observed in the biceps and triceps for the upper extremity in unilateral cerebellar lesions (A. Thomas).

2. Compression of the pons itself in cerebellopontine angle conditions is ascertained from the presence or absence of symptoms referable to the motor and sensory pathways which pass through the pons. Paresis or paralysis, anesthesia or analgesias or else paresthesias, changes of reflexes—all will be observed. The latter, particularly, are frequent. The knee jerks may be increased on the opposite side and not infrequently diminished on side of the lesion. The toe phenomenon and ankle clonus may be present on the side of the plus knee jerk.

3. The cranial nerves must be investigated with particular care. As the eighth, seventh, sixth and fifth nerves are most frequently involved, the following symptoms will be observed; anesthesia of the

face on the side of the lesion (fifth nerve); facial palsy of the peripheral type with all the characteristic symptoms (seventh nerve); paralysis of the external rectus muscle on the affected side (sixth nerve); unilateral impairment of hearing, also vertigo with a tendency to fall to the affected side (eighth nerve).

4. The vestibular test by the Bárány method has proven to be of considerable assistance in making a diagnosis of a pontocerebellar tumor, although in some cases it was shown to be unsatisfactory.

In the presence of such an array of symptoms, the diagnostic problem of pontocerebellar symptoms appears to be solved with great facility. If not all the abnormal manifestations are present at the same time, at least some of them will be found after a careful search. But this is not always the case. Exceptionally, one meets with unusual instances in which the described multitude of symptoms are not all present, and if only one or two symptoms of the very many are observed, one's thoughts may find themselves totally diverted from the idea of pontocerebellar condition. Seven such examples verified by necropsies are submitted. A minute examination along the plan described was made in each case. The results are as follows:

CASE 1.—Tumor involving right cerebellar hemisphere, extending forward into the cerebellopontine angle on the same side but not displacing or disfiguring the pontine region very much.

History.—Patient was first seen eight weeks before the operation and nine weeks before death. He complained of headache which, however, was not of an unusually severe character. His gait and station were normal; there was no trace of leaning to one side in walking. The knee jerks were equal and intact. The plantar reflex was flexor in type by several methods. The patient complained of occasional blurred vision but the eye grounds were normal. The eye muscles functionated normally. There was no history of syphilis and the blood Wassermann was negative. The diagnosis was exceedingly difficult in view of total absence of gross objective phenomena. The headache, it is true, was persistent, but it was present only about two months, and the patient continued his occupation of a truck driver until about one month before the operation.

Examination.—Repeated examinations were made. It was soon observed that while he was conversing or looking forward his head was slightly tilted toward the right side. During the subsequent days, and later on definitely, the head remained in the inclined position. Moreover, any attempt to incline it to the opposite side provoked some dizziness. He himself observed this when, accidentally, he would turn the head abruptly to the left side. The position of the head was such that the chin became directed toward the opposite shoulder. The patient soon commenced to complain of stiffness in the neck and careful interrogation revealed that this muscular stiffness was distinct on the right side but exceedingly slight on the left.

Diagnosis.—The persistent headache and the persistent unilaterality of the head position together with muscular discomfort on the same side gave an indication of the possibility of an intercranial neoplasm situated presumably on the right side and in the cerebellar area. This presumption became stronger when the symptom of the pointing reaction made its appearance. It was at first equal and normal on both sides. It is only during the later examinations that an error, at first slight and later distinct, was observed. The error con-

sisted of an outward pointing with the right hand. This position was invariably uniform at each of the examinations. The vestibular test by Bárány's method was negative.

Course.—Very soon the patient commenced to complain of frequent attacks of blindness lasting only a minute. The view of a right cerebellar involvement became stronger and stronger. The motor and sensory apparatuses remained intact throughout the entire period of observation. The eye grounds then showed no distinct pathologic lesions, but the veins commenced to appear to be somewhat dilated. A decompressive operation was advised and accepted. A mass was found as described above.

Fig. 1.—Tumor involving the right cerebellar hemisphere and extending forward into the cerebellopontile angle (Case 1).

Case 2.—Tumor situated in the right cerebellopontine area and producing no evident displacement of the pons with its structures. The mass encroached slightly on the fifth nerve.

History.—The patient, aged 46, bookkeeper, during the last two years of his life, suffered from pain in the right side of his face. The pain was not continuous, but would occur under the influence of some emotion or else with the change of temperature. The facial area involved corresponded to the distribution of the first two branches of the trigeminus. Objectively, there was a hyperesthesia of the entire right side of the face and particularly with regard to the test for cold. The pain was not of a neuralgic character, and not

occurring in paroxysms. The patient described it as a burning pain at one time, as a pulling pain at another. It was of a sharp character but of a steady and deeply seated aching. For many months the facial pain was the only morbid manifestation. There were no changes in the motor apparatus. Station, gait, reflexes, were all normal.

Examination.—The patient was repeatedly examined and carefully gone over. Three months before he died, for the first time there was noticed an error in the pointing reaction on the right side. His finger invariably would deviate outwardly. It became more pronounced as the disease progressed. At the same time a dysmetria made its appearance on the right side in the finger-to-nose

Fig. 2.—Section of tumor from Case 1.

test and remained unaltered until the end. One month before the termination the right knee jerk became diminished and remained as such. At no time did the eyes show any changes intraocularly or extraocularly. The vestibular test was negative.

Diagnosis.—The diagnosis had to be based exclusively on the persistent right sided facial pain, abnormal right past pointing, right sided dysmetria of the hand and diminished right knee jerk. For a long time, however, the few latter symptoms were not yet in evidence, and a diagnosis of a right pontocerebellar condition in view only of facial pain on the right side could not logically be entertained.

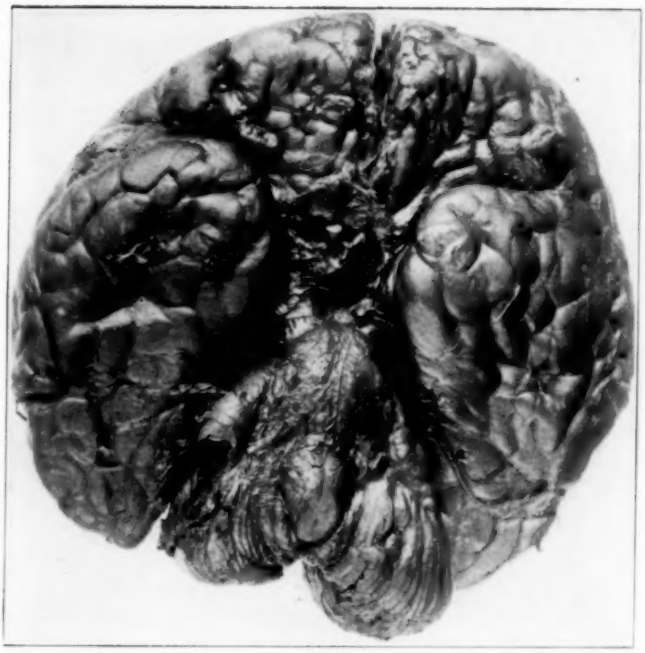

Fig. 3.—Tumor in right cerebellopontile angle (Case 2).

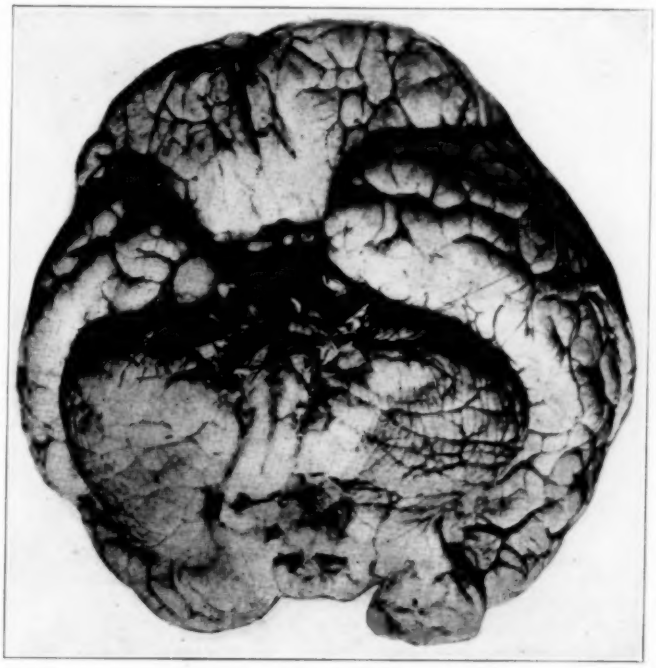

Fig. 4.—Small tumor in left cerebellopontile angle (Case 3).

Course.—The patient died from a virulent attack of pneumonia.

CASE 3.—A small tumor in the left cerebellopontine angle.

History.—The patient, female, aged 17, complained of occasional vomiting and headache during the past year. These symptoms would occur at the time of her menstrual periods. A relationship between the two phenomena as cause and effect was considered by several physicians who were called in for an opinion and advice. The patient was given intensive opotherapy for many months without relief. Two monhs before her death it was noticed that the left side of her face was slightly deviated toward the right side. This facial

Fig. 5.—Large cystic mass in right cerebellar hemisphere pressing forward against the pons (Case 4).

paresis presented all the characteristics of peripheral involvement of the seventh nerve.

Examination.—A careful examination revealed no abnormal manifestations in the motor or sensory apparatuses and no involvement of cranial nerves, except the seventh. It was observed, however, that the pointing reaction of the left arm was invariably inward. Many examinations were performed and the inward pointing on the left side was persistent while the pointing with the right hand was always correct. A vestibular test was negative.

Diagnosis.—In spite of the absence of gross symptoms, the past pointing together with the left facial paresis and the headache which became then more

persistent and continuous led to the thought of a left cerebellopontine pressure. No other symptoms were present during the last period of the patient's life.

Course.—A decompressive operation was performed, but the patient died three days later.

CASE 4.—A large cystic mass in the right cerebellar hemisphere pressing slightly forward against the pons.

History.—Patient, male, aged 40, complained of dizziness and a slight headache in the low occipital region for six months, also of a stiffness in the neck.

Fig. 6.—Large neoplasm in right pontocerebellar angle (Case 5).

Examination.—On examination it was noticed that his head was slightly tilted to the right and on attempts to turn it toward the left side he would become dizzy. The dizziness would last about one minute. The motor and sensory apparatuses, as well as the special senses, were all normal.

This condition lasted two months without alteration. Soon a new symptom made its appearance—the patient complained of occasional diplopia. The eye grounds as well as the ocular muscles remained intact. On repeated examinations an error of pointing reaction was observed in the right arm, namely inward and downward. A vestibular test was negative.

Diagnosis.—The headache (though not severe) in the suboccipital region, cervical discomfort, dizziness, slight tilt of the head to the right and faulty pointing reaction—were the only symptoms for a diagnosis. Since these phenomena were uniformly persistent, a tentative diagnosis of a right cerebellopontine lesion was made.

Course.—The patient met with an accident falling down a flight of stairs and fractured his left thigh. On the third day he developed a violent type of pneumonia and he died on the fifth day.

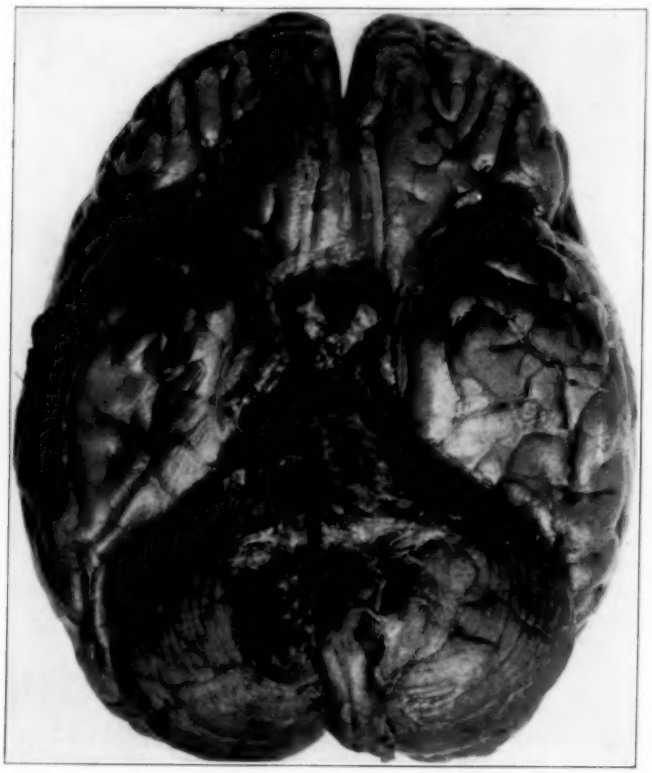

Fig. 7.—Small tumor in anterior portion of right cerebellar hemisphere lying close to the pons anteriorly (Case 6).

Case 5.—A large neoplasm in the right pontocerebellar angle pushing the pons to the left.

History.—Man, aged 38, teacher of languages, complained for several years of attacks of vomiting, followed by severe headache which would last twenty-four hours. At first they occurred once in two or three months, but within the last year of his life, approximately once in two weeks.

Examination.—On examination made six months before he died a slight engorgement of the retinal veins in the right eye with two hemorrhagic spots

in the left eye were noticed. The motor and sensory apparatuses were intact with the exception of a mild but a distinct hyperesthesis over the right side of the face. No other symptom was in evidence until two months before death. He then showed defective pointing reaction in the right hand with outward direction.

Diagnosis.—The diagnosis was quite difficult at first in view of the facial hyperesthesia being virtually the sole objective symptom. Nevertheless, the

Fig. 8.—A mass lying in the anterior portion of the left cerebellar hemisphere close to the pons and adherent to the eighth nerve.

persistence of it, together with the history of headache and vomiting (although only paroxysmal) gradually led one to suspect an intracranial condition. The appearance of the pointing reaction, which remained persistently confined to the right side, fortified me in my suspicion.

Course.—A month later hemorrhages appeared in the right fundus oculi, and the patient complained of losing his eyesight. A right suboccipital decompression was performed but the patient died on the following day.

CASE 6.—A small tumor of the size of a walnut in the anterior portion of the right hemisphere lying close to the medulla laterally and the pons anteriorly.

History.—Patient, woman, aged 48, gave a history of prolonged headache of a very mild character occurring once a month during a period of six years which was diagnosed as migraine. When I saw her, about six months before death, she presented a slight palsy of the external rectus muscle on the right side, disturbances of smell in the right nostril and some discomfort in the neck on both sides, which she qualified as a pulling sensation. The reflexes, sensations, gait, station were all normal. She complained of dimness of vision but the eye grounds were normal. This condition remained unchanged for four months when error in the pointing reaction of the right hand was noted: its reaction was outward and downward. This error persisted until the time of death. During the last three weeks a tilting of the head to the right was noticed and remained unaltered until the end. An operation was declined.

Course.—Patient contracted a profuse diarrhea with a bloody discharge and died suddenly. She was found dead in bed.

CASE 7.—A mass lying in the anterior portion of the left cerebellar hemisphere close to the pons and adherent to the eighth nerve. During the removal of the brain the affected hemisphere was much lacerated.

History.—Patient, male, aged 45, a bartender by trade, complained during the last two years of his life of headache and occasional vomiting and occasional diplopia. He came under my observation two months before death.

Examination.—He presented a tilting of the head to the left with the chin turned to the right. When the head was turned to the opposite side, dizziness would appear but it would last but a few seconds. With the exception of a markedly diminished left patellar tendon reflex there were no other evidences of an intracranial involvement. A vestibular test at that time was negative. Soon the pointing reaction became defective: its direction was inward and downward.

Diagnosis.—The clinical picture was merely suggestive of a cerebellar condition.

Course.—One month before the operation the patient suddenly became blind in his right eye. An examination revealed a marked veinous engorgement with a few hemorrhagic spots in the right ocular fundus but no changes were seen in the left eye. A Bárány test at this phase was positive and indicated the existing of a pontocerebellar lesion. A decompression was made in the suboccipital region, but the patient expired a few hours later.

DISCUSSION

An analysis of these cases demonstrates one striking fact, that while during many months no diagnosis could be made, the symptoms suggesting a pathologic condition approximately in the cerebellar vicinity commenced to make their appearance very late, so that early surgical interference could not be thought of. As to the symptoms themselves, their number was too small to permit strong inferences at first, but it is only because of their unilaterality and gradual and progressive development one after another, finally their persistence, after once having been established, that a tentative conclusion was reached as to their localization. It is not less remarkable that in five of the seven cases the increased intracranial pressure failed to produce changes in the ocular fundi. In the two positive cases, the changes appeared only a short time before death (two months and one month,

respectively). Retinal hemorrhages, with venous engorgement, were the symptoms observed. In view of their late development, the early diagnosis remained in suspense. Their entrance into the picture of the disease at once rendered the tentative localization already made more and more suggestive.

The positive sign common to all the cases was the error in the pointing reaction. The latter seems, therefore, of great value, and the search for it should be made persistently and repeatedly since in each of the seven cases it was a late manifestation; its absence in the early period of the disease was noticeable.

A special position of the head was present in four of the seven cases. The head was inclined toward the side of the tumor and when attempt was made to move it to the opposite side, headache and dizziness appeared, a diagnostic symptom to which I directed attention several years ago and which I had opportunity to verify on many occasions.[1] The special position of the head, which remained unaltered until death, contributed, to a great extent, to the formation of a diagnostic opinion which was so difficult in view of the extremely small number of symptoms.

In two cases there was a persistent discomfort in the neck muscles consisting of a stiffness or of a pulling sensation. Although such a phenomenon has been observed, and reported in the literature, nevertheless, its inconspicuousness in both cases did not permit of attaching any diagnostic importance to it.

In Case 2 one symptom aroused a strong suspicion with regard to an intracranial involvement, in spite of the absence of gross and definite manifestations. This was a persistent pain with an objective hyperesthesia confined to the area of distribution of the first two branches of the fifth nerve. The pain was not of a neuralgic character but was a deep seated and continuous aching, pulling, or burning. It was so unmistakably different from the classical neuralgia and so persistent and so discomforting to the patient that attention was unavoidably directed to the possibility of an intracranial involvement.

Nerve involvement is observed very frequently in cerebellopontine neoplasms. Indeed, one may say, it is a strong diagnostic and localizing symptom. Curiously enough, only in two cases of my series the seventh and sixth nerves, respectively, were affected, but in a mild degree and only toward the termination of the disease. A very long period of time elapsed before these two nerves showed any involvement at all, and no definite diagnosis could be made from the very few symptoms present.

The vestibular tests by Bárány's methods are usually of considerable assistance in pontocerebellar conditions. The negative results

1. J. A. M. A. **50**:461 (Aug. 8) 1908.

observed in six cases of the series are certainly striking. In one case it proved to be confirmatory of its diagnostic value during the advanced period of the disease. It seems, therefore, that in cases in which there is a great paucity of symptoms, the vestibular test itself is negative, although its usefulness would have been particularly enhanced in such cases had it given positive results.

CONCLUSIONS

This study indicates the possibility of unusual difficulties being present in the diagnosis of pontile angle tumors, and, therefore, leads to a delay in operative procedures, which, after the diagnosis has been made possible, become useless and highly dangerous.

The vestibular reactions which ordinarily render considerable aid in the diagnosis of pontocerebellar tumors are evidently not invariably positive in every case. Their absence, singularly enough, coincides with the absence of many other important symptoms on which a neurologic examination is based. The present study demonstrates the fact that integrity of vestibular reactions does not exclude the possibility of a pontile angle tumor.

In cases in which the diagnostic difficulties are great, one or two slight manifestations may obstinately persist at repeated examinations; such symptoms, although slightly or very slightly developed, should be regarded with suspicion, and if they are persistently unilateral a pontocerebellar condition should be thought of. Furthermore, the cases under discussion show that among such apparently insignificant symptoms the pointing error is of great localizing value, as it was present in each case. Its value is parallel with that of gait disturbance which is manifested in walking or falling toward one side in unilateral cerebellar conditions; it is also parallel with diadokokinesia (quick pronation and supination) which is intimately related to the functioning of the homolateral cerebellar hemisphere. The pointing errors are to be regarded as the result of consequences of a disturbance in the regulation and in the coordination of voluntary movements, which are controlled by the cerebellum, directly or indirectly; the rôle of the latter as a coordination center, or as an organ receiving its reflex influence on coordination from elsewhere in the central nervous system, is still in dispute.

Persistent pain in the area of distribution of one or two branches of the trigeminus, pain which is not of the typical neuralgic character, but has the character of pulling, burning, boring, etc., seems to be a highly suggestive symptom in the conditions under discussion, as Case 2 has proven. Here, again, its persistence at repeated examinations, and, particularly, its extremely deep seated character, should

lead to the possibility of a material pressure on the fifth nerve at the level of the pons. Its occurrence in Case 2 seems to be highly instructive for diagnostic purposes.

After a careful consideration of all these special phenomena, it appears that while it is true that a diagnosis is almost an impossibility in the presence of such an extremely small number of symptoms as seen in this series of seven cases, nevertheless, the analysis of the special symptoms with their particular characteristics even in the early phases of the disease is bound to arrest attention. In all such cases a cerebellopontile condition should always be thought of and early radical intervention be considered seriously. To reiterate: a negative vestibular test is not to be relied on for diagnosis as it is not conclusive and this study has shown that integrity of vestibular reactions coincide frequently with paucity of other neurologic manifestations.

Special emphasis is laid on this important fact that a limited or very limited number of morbid manifestations may be present even in cases in which the tumor is of a large size, as the findings in these cases have proven it amply. The dimensions, therefore, of a neoplasm must not be taken into consideration in every case when the proper estimation of the few symptoms present is diagnostically figured out.

H. W. Stenvers recently called attention to a very interesting differential diagnostic point. He observed in several instances that roentgenograms show erosions of the mesial part of the petrous bone in pontile angle tumors. If this statement is correct, these findings are of great practical value and add an important diagnostic symptom, particularly in cases in which the number of symptoms is unusually small.[2]

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2. J. Nerv. & Ment. Dis. **55**:54 (Jan.) 1922.

OSTEOMALACIA *

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Osteomalacia is a generalized softening of adult bones which were at one time quite calcified and hard. It occurs in adult man and in some animals and birds. In man several types are recognized.

1. A mild form is found in pregnant, puerperal and lactating women, which recurs with each pregnancy. The skeletal changes become worse with each attack, but tend toward a spontaneous recovery when the drain of pregnancy and lactation is removed. A very similar group of cases arises in famine districts, or when the variety of diet is limited. The avidity of the tissues for calcium and phosphorus in these forms of osteomalacia is, however, undisturbed, and when these elements are added to the dietary in usable form, the patient recovers.

2. A second or senile type occurs in old people, in which the bone softening is, as a rule, confined to spine and pelvis. It generally progresses rapidly for a time, then ends in recovery with marked residual deformity.

3. A severe form occurs in pregnant, puerperal and multiparous women, in boys, men and castrated women, which is steadily progressive and shows no tendency toward recovery, ending in a marasmic state.

In lower animals practically all cases examined were of this last type. It occurs equally in male and female, mammal and bird. Up to the present time there have been forty-nine cases among mammals and thirty-four among birds. Considering the many species of animals exhibited, the disease is rather sharply limited to a very few groups.

TABLE 1.—CASES OF OSTEOMALACIA IN MAMMALS AND BIRDS

MAMMALS	Cases	Males	Females
Primates	26	19	7
Lemurs	4	0	4
Carnivora	6	4	2
Hyraces	1	0	1
Rodentia	5	3	2
Marsupialia	8	5	3

AVES	Cases
Columbae	12
Galli	9
Psittici	6
Passeres	2

This table shows that 50 per cent. of all the mammals infected are primates, and in this order are limited almost exclusively to the Cebidae.

* From the Laboratory of the Philadelphia Zoological Society.

Of the birds 40 per cent. are doves (Columbae), 30 per cent. are pheasants (Galli), 12 per cent. parrots (Psittici). In the first two groups the disease is very extensive, involving practically every bone in the body, and the lesions are much more severe than those found in any of the other groups of animals or birds. Many other animals exposed to exactly the same environmental condition show a real or apparent immunity. Necropsy findings are practically the same in birds and mammals.

In mammals, the long bones of the extremities are early and seriously involved. They yield under the weight of the adult body, twist and bend, causing extraordinary and grotesque deformities. Very soon the animal is unable to stand (cage paralysis).

In birds, the more serious lesions occur in the bones of the thorax, ribs and sternum. Claws and beak are frequently affected, often so softened that the bird is unable to pick up seeds.

The gross appearance of the bones is again roughly similar. The skull may be reduced to the consistency of writing paper, the margins of the bony plates are often markedly thinned, while centers show irregular spots of thinning interspersed with areas of thickening. In one case, an adult Cebus, the skull was so completely deprived of calcareous matter that it could be twisted. The ribs are irregularly softened. Thin translucent areas are found associated with white opaque fusiform or nodular beadings, especially at the costosternal junction and at the epiphyses. These beadings are apparently efforts at splinting, occurring where the weakness from excessive bone absorption is the greatest. The whole rib may be soft, the consistency of soft rubber, and almost entirely deprived of the bone salts. It will cut with scarcely any crunch and bend easily in the fingers.

The long bones show the same irregular thickening closely associated with areas so thinned that they are almost translucent. They are usually distorted because of the body weight, generally a forward bowing. Fractures are extremely common; often more than one is found at necropsy. These injuries may show no attempt whatever at repair, or more often a fibrous or inadequate cartilaginous union. In all instances the deposition of bone salts is very inefficient. More rarely there may be an overactive effort at repair, but here also with only a scanty deposition of bone salts. In the immediately adjacent areas there may be marked subperiosteal reaction, but, as a rule, the periosteum shows no reaction at all.

In man, the small joints often become deformed early and in appearance suggest an osteo-arthritis. Large joints may ankylose. The spine and pelvis are involved sooner or later, ending often with a total loss of power over the legs.

Besides the bone lesions, there is constantly present in these animals a more or less severe secondary anemia, a lowered alkalinity of the blood and a fermentative type of intestinal indigestion. All show slight dilatation of the stomach, with some atrophy of walls. The small intestines are thin walled, and the accumulation of gas gives to it a sausage appearance. Lactic acid was found once in the urine. The kidneys show mild nephritis changes, and in some, fatty degeneration or merely pallor is present.

Microscopically, the bones show in every case a more or less pronounced absorption of the calcareous salts (osteoporosis) and with the abnormal bone absorption there is a marked tendency toward the deposition of newly formed osteoid tissue in which calcification never reaches the normal. Sections show osteoid margins along each lamella of bone, covering in the parts still calcified. Normal lamellar arrangement of bone is sometimes retained; usually, however, the bone cortex is very thin with coarse, broad trabeculae, wide marrow spaces and only the slightest tendency toward the formation of Haversian systems. Lacunae and osteoblasts may be normal but contain little calcareous matter. Osteoblasts and osteoclasts may be few, equal in number, or the osteoclasts may be unduly numerous. Osteophytes and Sharpey's fibers, similar to those found in osteitis deformans, are frequently seen. Cancellated tissue is often much decreased, especially at the ends of the long bones. In some cases it has practically disappeared.

The periosteum may be sharply marked off from the bone cortex; as a rule, it shows no activity in its osteogenetic layer. The subperiosteal bone may be very thin, almost like paper, but normal in appearance. At the junction of the bone and the cartilaginous rib there is often a thickening, seemingly from the periosteum. Endochondral bone formation at the epiphysis is usually abnormal, as shown by its irregularity of foci and extremely large intratrabecular spaces; osteoblasts are numerous. The marrow cavity is wide and filled with red more or less edematous marrow. The bone marrow is very much like that found in aplastic anemias. It is generally scanty and collected near the ends of the bones. Bone shows active removal of old trabeculae by means of numerous osteoclasts, and the production of fibroblasts, some of which differentiate into bone cells for forming new trabeculae in which only scanty amounts of lime are deposited. Rarely ever is normal bony architecture reproduced.

An analysis of the bones shows a marked diminution in the amount of calcium and an excess of sulphur and magnesium. Metabolic studies show a loss of calcium primarily in the feces, but also a marked increase in the calcium output in urine, with the retention of sulphur and magnesium. A salt metabolism of one monkey was attempted on four four-day periods, which showed a high calcium and phosporus loss with a moderate magnesium and sulphur retention.

No hypothesis yet advanced satisfactorily explains the observed facts. The one most generally accepted is Fehling's [1] theory, based on Forchier's observation that osteomalacic women were improved or cured by the removal of the ovaries. His idea was that the disease was due to a hyperfunction of the internal secretion of the ovaries, which produced a sympathetic paralysis of the vasomotor system, which, in turn, caused a hyperemia of the bones and a consequent abstraction of calcium. Careful examination of our autopsy material failed to reveal any specific or distinct lesion in the ovaries, or in any of the ductless glands. All were, however, apparently smaller than glands usually found, with the exception of the adrenals, which were either normal in size or larger, and in two cases much congested. Minor changes were noted in the thyroid in a few instances. Ovaries and testicles were grossly normal in appearance. Microscopically, spermatazoa were found to be much reduced in numbers.

The second theory of origin was that in some manner the alkalinity of the blood was decreased, which permitted the lime salts to go into solution. This decreased alkalinity might be due to (1) a primary ductless gland disorder, especially a dysfunction of those glands which in some manner were concerned with bone metabolism; (2) a loss of alkali; (3) an excessive acidity, either the result of a predominantly acid forming diet, or due to an excessive production of acid in the body. These factors might act independently or in coalition, and might act directly or indirectly through their influence on the ductless glands. The absorption and deposition of salts are dependent on the chemical equilibrium of the cells, and slight shiftings of the acid base equilibrium of the cells in either direction may be sufficient to cause extensive lesions.

In favor of this view are many observations and experiments. Virchow [2] described deposits of calcium in the organs of people dying of osteosarcoma, osteomalacia and other disease states in which there is excessive bone absorption. These deposits were found in all organs, but especially those excreting an acid into their cavities—lungs, stomach and kidneys. In these organs there was no evidence of diffuse necrobiosis previous to the deposit of the lime salts. It seems probable, therefore, that the calcium was precipitated into the normal organ because the excretion of the acid in these parts left the tissue fluids relatively more alkaline and less able to hold the same amount of calcium in solution. Pawlow [3] found a bone condition very similar

1. Fehling: Ueber Wesen und Behandlung der Osteomalazie, Arch. f. Gynaek. **28**:1890; **29**:1891.
2. Virchow: Virchows Arch. f. path. Anat. **197**:112, 1909.
3. Pawlow, cited by Babkin: Ztschr. f. Stoffwechsel **11**:561, 1910.

to osteomalacia in dogs, in which a pancreatic fistula was continued for long periods. Here there was a constant loss of alkali through the fistulas, and the body alkalis had to be utilized for neutralization of the acid production.

Diet has at various times been proposed as a factor, at least, in the production of this condition. This idea has gained considerable weight through the increase of the number of cases recorded from famine districts and parts of Central Europe where the dietary is restricted and unbalanced. Voit [4] fed pigeons for one year on diets very poor in calcium, with clinically no ill effects, but found at necropsy marked wasting of the sternum and skull.

In adults a poor calcium diet can be continued for long periods without any apparent ill effect, because the losses from the blood and soft tissues can be replaced from the bones. In the young, however, poor calcium diets very promptly cause weakness and flexibility of the bones.

During pregnancy the calcium requirements of the animal are markedly increased. Steenbock and Hart [5] found that the production of milk made heavy drains on the skeleton, unless the amount of calcium and phosphorus contained in the food was abundant. Forbes and Beegle [6] also noted that calcium was often lost when the animal was storing nitrogen. Steenbock [7] and his associates have produced osteomalacia in cattle by feeding them "shorts," a diet high in magnesium but otherwise well balanced. Sherman and Gettler [8] found, on a diet giving a high acid ash, as rice and potatoes, that 33 per cent. of the acidity could be accounted for by increased ammonia production and about 40 per cent. by the increased acidity of the urine, leaving a remainder which must be eliminated or neutralized by sodium or potassium carbonate of blood or other fixed alkali. Etienne [9] found that excess of magnesium in an otherwise well balanced food apparently caused a continual loss of calcium. Schiff and Strausky injected subcutaneously a magnesium salt and produced a marked increase in calcium output in urine and a diminution in calcium retention. In children after weaning, calcium disturbances are frequent and often are due to disorders of digestion and obscure irregularities of nutrition.

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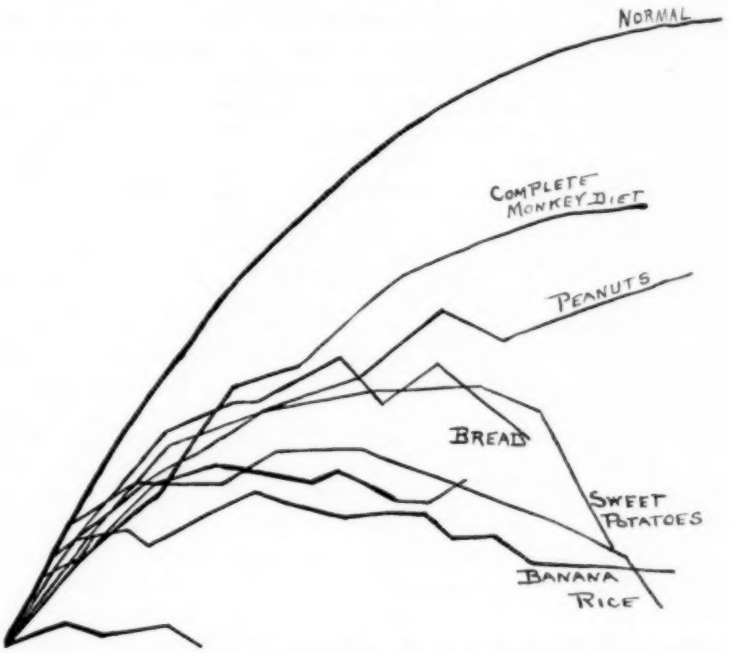
4. Voit, E.: Significance of Calcium in Animal Nutrition, Ztschr. f. Biol. **16**:55, 1880.
5. Steenbock and Hart: Influence of Function on the Lime Requirements of Animals, J. Biol. Chem. **3**:23, 1913.
6. Forbes and Beegle: Mineral Metabolism of the Milch Cow, Ohio Agriculture Experiment Stat. Bull. 295.
7. Steenbock and Hart, Development of Osteoporosis by Swine Induced by High Magnesium Intake, J. Biol. Chem. **3**:23, 1913.
8. Sherman and Gettler: The Balance of Acid Forming and Base Forming Elements in Foods and Its Relation to Ammonia Metabolism, J. Biol. Chem. **11**:323, 1912.
9. Etienne: J. Physiol. et Path. **14**:108, 1912.

From these observations and experiments, it seemed advisable, first, to examine carefully the diet of the Cebidae monkeys, in which family the disease was most prevalent and most severe. The food of these monkeys, two bananas or two apples or six small sweet potatoes, with a portion of boiled rice about the size of an egg; occasionally bread, peanuts and lettuce. This diet was studied first, for the amount of essential protein, fat, carbohydrate and ash; then, for the general character of the protein and ash; and third, for the ability of this entire diet and of each of its constituents to maintain normal growth, health and



The average growth curves are plotted for the entire time on which the rats were fed the separate constituents of this diet and they are compared with the curve of normal rats on a well balanced diet and with rats on the complete diet fed to these monkeys.

reproduction. A diet is considered normal when it maintains a normal weight curve, gives a normal immunity to disease, allows completion of a normal span of life, and allows normal breeding of healthy young that shall be vigorous when weaned.

Analysis of this diet computed from Atwater's tables and by actual analysis of the amounts of food consumed by the animal in four four-day periods gave: (1) Protein low in quantity and poor in quality;

especially low in phosphorus content. (2) Fat very low. (3) Carbohydrate very high, almost eleven times the value of all other ingredients. (4) Ash decidedly low and predominantly acid. Further analysis of this ash showed only a trace of calcium and phosphorus and iron; only a small amount of sodium and potassium; sulphur and magnesium were slightly higher. (5) Vitamins A, B and C were present in extremely small amounts. Vitamin A was exceptionally deficient and in the rations of some days was entirely lacking.

The accompanying graph shows the effects of the separate constituents of this diet and the diets as a whole on the growth and nutritive balance of rats. Rats were chosen for this study because they were susceptible, and the only animal for which we have normal standards for comparison. Lettuce, corn and apples did not support life; bananas gave little growth with no reproduction, but life continued for a considerable length of time. Eggs were extremely detrimental to the health of rats, causing diarrhea with many fatty acids in the stool, eczema and early death. Sweet potatoes caused distention of the abdomen, sore eyes, diarrhea with frothy stools, rough coarse fur, hump back, no breeding and considerable atrophy of testicles. Rice produced a loss of weight, constant diarrhea, hump back, swollen joints, sore eyes and no breeding. With bread the general condition was good; weight curve depressed and diarrhea frequent. Reproduction was much reduced. The young died or were eaten by parents before weaning. With peanuts the eyes were sore, a diarrhea frequent, but coat was fair and general condition good. The rats bred poorly and the young all died before weaning. In other words, not any constituent of the diet was able in itself to support life and health. The entire diet gave a generally good condition, with a moderate depression of weight, immunity and breeding. Frothy diarrhea was present in most of the rats at some time during the experiment, and in some was constant. Litters were vigorous at birth but were always eaten by the parents.

A second series of rats was subjected to the principal ingredients of this diet for one month and was then fed with additional food which, theoretically, should replenish the deficient diet and make it adequate, as shown by resumption of normal growth curve.

Table 2 shows the additions necessary for corrections of the separate ingredients of the diet.

The complete diet was rendered adequate by the addition of fresh, whole milk and leafy vegetables, or by butter fat, salt mixture and leafy vegetables.

In this monkey diet several factors are of importance: (1) Low vitamin content, especially vitamin A, factors which are essential for life and growth. (2) A high carbohydrate diet which on oxidation

TABLE 2.—CORRECTION OF DIET INGREDIENTS

DIET	CORRECTED BY
Rice	casein, salt mixture, carrots or lettuce, butter fat.
Bread	casein, butter fat, salt mixture, especially phosphorus.
Potato	salt mixture, especially sodium chlorid and calcium carbonate.
Raw peanuts	salt mixture.
Bananas	casein, yeast or carrots.
Corn	casein, tryptophan, lactalbumen.
Egg	detrimental to rats; no recovery.
Apple	casein or gelatin, butter fat.
Onion	casein or gelatin, butter fat.

yields an acid ash and which favors the growth of intestinal bacteria producing acid and gas. The acid from these two sources must be neutralized either by the alkalis derived from food or from the body storage. This diet, however, is abnormally low in ash, and especially in the alkaline salts of the ash, therefore making it an ideal diet for the production of osteomalacia.

The full significance of predominantly acid forming diets has only lately been fully recognized, especially as they affect protein storage, and, therefore, growth and recuperation by deflecting the nitrogen and draining the body alkalies. Goto shows that in experimental acidosis the carbonates are first called on, next, the alkali phosphates, particularly the potassium phosphate of muscles and calcium carbonate of bones.

The main service of milk is probably due to its alkaline residue when oxidized in the body, and its plentiful supply of calcium, iron and vitamins.

This diet is deficient in those salts that were lacking in the bones of the monkey and which the animal was excreting in excess of its intake, possibly because of the excess of magnesium.

This ration at best would only keep the animal in calcium and phosphorus equilibrium, and any upset making even the slightest demand on its alkaline storage would be sufficient to set up a faulty metabolism.

CONCLUSIONS

It would seem that in this inefficient diet lies, if not the cause of osteomalacia, at least a very potent factor in its production.

1. The disturbance of the calcium and phosphorus metabolism may be due primarily to the deprivation of the alkaline salts from the diet (famine osteomalacia); or, second, to a drain from the alkaline storage of the body, associated with a deficient diet, as in the cases of osteomalacia of pregnancy and lactation; or, third, in the combined action of a diet faulty in more than its salt content, which, by the production of acid in its oxidation and by favoring the development of acid

forming bacteria, causes a drain of the body alkali for the neutralization of this acid; or, fourth, and this is more probable, especially in the severe form, it is due to the combination of all these factors acting upon the ductless glands and through them altering definitely the inorganic metabolism.

2. In severe osteomalacia the power to retain and absorb calcium and phosphorus is practically lost, while in the cases developing during famine, and in pregnancy and lactation, this power is retained. These subjects immediately recover when calcium and phosphorus are presented in usable form. This permanent loss of power to absorb or retain calcium and phosphorus can be explained only by some definite changes in the endocrine balance.

3. It is important, also, that while this disease is very common among the Cebidae it has never been found among our Macaques. This may be due to the fact that owing to the storage sacs in the mouth of the Macaques more food proportional to body weight is consumed; and to a probable essential difference in the basal metabolism of these families and individuals. All the factors enumerated do tax the metabolic resources of the body and depress the functions of the endochrine glands. Detailed and accurate quantitative studies of normal metabolism and their effect on the ductless glands will alone give a more definite answer to the problem. The starting point of treatment must be a diet adequate in vitamins and containing a proper inorganic balance.

THE ALKALI RESERVE IN "ROENTGEN-RAY SICKNESS" *

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Ever since the introduction of roentgenotherapy in medicine, constitutional reactions following irradiation have been observed. These reactions are manifested clinically by symptoms which may appear any time after irradiation, from a few minutes to a day or more, usually from four to six hours, and which may run the gamut from slight headache and malaise, anorexia, nausea and vomiting to complete prostration, compelling the patient to remain in bed two or three days. Ordinarily, the symptoms subside in a few hours.

The exact cause of these manifestations is not known. Several theories as to their origin have been offered, the merits of which, with one exception, it is not the purpose here to discuss. Lange,[1] on the basis of the fact that the administration of sodium bicarbonate seemed to ameliorate or to prevent the onset of postirradiation symptoms, suggested that acidosis might be the cause. It is assumed that the term "acidosis" was used in the ordinary sense as meaning a lowered alkali reserve. This theory appeared to have some experimental substantiation in the work of Denis, Martin and Aldrich.[2] These workers showed that a large dose of roentgen rays, lethal when applied over the abdomen of rabbits, was not fatal when applied over the chest or legs with the abdomen protected, and that the blood of the former animals showed a lowered alkali reserve. They state, "The results suggest the hypothesis that acidosis may be a factor in 'treatment sickness' following abdominal irradiation." However, as they point out, the dose applied over the abdomen of these animals was large enough to be fatal, about five times the amount usually given any one portion of a patient's body, and, whereas clinical "treatment sickness" appears a few hours after irradiation, no objective symptoms appeared in the rabbits for several days. It should also be noted that the reduction in alkali reserve in these experiments did not occur for several days after irradiation and that the most marked lowering seemed to be a terminal affair.

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* From the Department of Medicine, Harvard Medical School, and the Medical Service of the Peter Bent Brigham Hospital.

1. Lange, S.: The Cause and Prevention of the Constitutional Symptoms Following Deep Roentgen Therapy, Am. J. Roentgenol. **3**:356, 1916.

2. Denis, W.; Martin, C. L., and Aldrich, M.: A Study of the Relative Toxic Effects Produced by Regional Radiation, Am. J. M. Sc. **160**:555, 1920.

Following the intravenous injections of radium deposit in dogs, Theis and Bagg [3] found that the nitrogen elimination was increased and that examination of the nitrogen partition showed that ammonia was increased proportionally more than urea, suggesting an acidosis. It is of interest that these dogs manifested symptoms very similar to those following heavy roentgenotherapy.

During the fall and winter of 1920-1921, numerous patients in the roentgen-ray treatment clinic of Dr. George W. Holmes at the Massachusetts General Hospital were advised to take sodium bicarbonate for the nausea following treatment. No definite benefit seemed to result. Similar observations were recorded by Pfahler.[4] In December, 1920, an opportunity presented itself to study the reaction of the blood of a patient undergoing irradiation. A man (J. J. M., W. S. 239,973, aged 28) with metastatic carcinoma of the peritoneum and mesentery of unknown origin (operative diagnosis), who had received frequent roentgen-ray treatments during the preceding seven months, was readmitted to the West Surgical Service of the Massachusetts General Hospital in order to keep him under observation while undergoing intensive roentgen therapy. This patient usually had nausea and vomiting after irradiation and was sometimes compelled to remain in bed during the reaction. Dec. 14, 1920, three days after a treatment over an abdominal area, venous blood was drawn into a test tube containing a crystal of potassium oxalate. The carbon dioxid combining power of the plasma was determined by Miss Margaret Woodwell in the laboratory of Dr. J. H. Means and found to be 78.5 volumes per cent. December 15 another abdominal area was irradiated. About three hours later, during the postirradiation nausea, venous blood was drawn in the same way and the carbon dioxid combining power of the plasma found to be 80 volumes per cent. About twenty-six or twenty-eight hours after the next treatment, the carbon dioxid dissociation curve of the blood of this patient was determined by Dr. J. H. Means and Dr. A. L. Barach, to whom I am greatly indebted for this data, and the hydrogen-ion concentration was found to be normal (p_H. 7.35). The carbon dioxid content of the arterial blood (whole blood) was 54.5 and that of the venous blood 60 volumes per cent. Another patient (F. C., W. S. 237,990, male, aged 32) with metastatic melanosarcoma, who had received frequent heavy treatments over the abdomen for five months, showed a plasma carbon dioxid combining power of 80 volumes per cent., the blood being taken in oxalate one half hour after irradiation before nausea had begun.

3. Theis, R. C., and Bagg, H. J.: Effect of Intravenous Injections of Active Deposit of Radium on Metabolism in the Dog, J. Biol. Chem. **51**:525, 1920.

4. Pfahler, G. E.: The Cause and Prevention of the Constitutional Effects Associated with the Massive Doses of Deep Roentgen Therapy, Am. J. Roentgenol. **5**:5, 1918.

The results on these two patients indicated that there was no fall in the alkali reserve after irradiation. In fact, the figures for the plasma carbon dioxid combining power are unusually high, as both 75 and 80 volumes per cent. have been recorded as the upper limits of normal. To secure more evidence, animal experiments were planned with the idea of determining whether or not relatively moderate doses of roentgen rays were followed by the clinical signs of "treatment sickness" and by a lowering of the alkali reserve of the blood. These experiments were carried out during the fall and winter of 1921-1922 at the Peter Bent Brigham Hospital. Further clinical observations were made as opportunities presented themselves.

The plasma carbon dioxid content of two dogs receiving weekly irradiations was studied over a period of about three months. Dog 1 was a black and white mongrel weighing 12 kilos. Dog 2 was of airedale extraction, not quite full grown, and weighing 10.3 kilos. Dog 3, a yellow mongrel weighing 11 kilos, was kept as a control under the same conditions as the other two dogs and received no radiation until this experiment was finished, as described below. The radiation was applied over the upper part of the abdomen for the first two or three times and then alternately over the back and over the upper abdomen, always involving the viscera of the upper two-thirds of the abdomen. The rays were produced by a broad focus Coolidge tube activated by an interrupterless Victor-Snook transformer, using a spark gap of 9 inches between spheres, a filter of 5 mm. of aluminum and a target-skin distance of 8 inches. With this setting 50 milliampere were at first given to both dogs. This quantity of radiation was sufficient to make Dog 1 vomit once or twice in two or three hours and to refuse food. Dog 2, on two trials with 50 ma. minutes and one with 60, gave no evidence of a reaction. However, 75 ma. minutes were sufficient, with one exception, to make him vomit once. The animals were bled from the external jugular vein at varying intervals after irradiation, the blood being collected under liquid petrolatum in a tube containing a crystal or two of potassium oxalate. It was then transferred to a centrifuge tube and centrifuged under oil. The carbon dioxid content of the plasma was determined by Van Slyke's method (1917).

The blood bicarbonate in dogs apparently has lower normal limits than in man. Hjort and Taylor[5] found the plasma carbon dioxid combining power of apparently normal dogs to vary from 42.9 to 67.3 volumes per cent. in twenty-four animals. The blood was not manipulated under oil and the plasma was equilibrated with air containing 5.5 per cent. carbon dioxid. I found that the plasma of dog blood

5. Hjort, A. M., and Taylor, F. A.: The Effect of Morphin on the Alkali Reserve of the Blood of Dogs Gassed with Fatal Concentrations of Chlorin, J. Pharmacol. & Exper. Therap. **13**:497, 1919.

taken and centrifuged under oil gave off, on the average, from 7 to 8 volumes per cent. more carbon dioxid after equilibration with my own alveolar air than before, i. e., the actual carbon dioxid content of dog plasma was from 7 to 8 volumes per cent. less than the carbon dioxid combining power when equilibrated with presumably normal human alveolar air. In view of the reaction which takes place between plasma and corpuscles when carbon dioxid is lost from the blood, which results in a slight decrease in the amount of plasma bicarbonate, and in view of the subsequent equilibration with carbon dioxid at about the tension of human alveolar air, the method used by Hjort and Taylor undoubtedly gave figures slightly higher than the actual plasma carbon dioxid content. In several determinations of the plasma carbon dioxid content of two normal dogs, the blood being collected under oil, Gauss [6] found one 43.8 volumes per cent. and one, when the animal was excited, as low as 40.9 volumes per cent. Therefore, one could hardly say that the alkali reserve of dog blood was below normal limits unless the carbon dioxid content of plasma handled under oil went below 40 volumes per cent., which is probably a conservative estimate.

Two preliminary determinations of the carbon dioxid content of the plasma were made before any radiation was given. On Dog 1 the second of these and the first after irradiation was begun were not made with the animal fasting. Chanutin [7] has shown that the ingestion of a quantity of meat raises the carbon dioxid combining power of dog plasma from 5 to 9 volumes per cent., the peak coming anywhere from one to four hours after the feeding. The remainder of the observations were made with the animals fasting, except for the last on Dog 1, just before he was etherized, as necropsy showed the stomach to be full of undigested meat. This final observation, nine days after the last irradiation, was the only one in which the alkali reserve was lowered definitely below the normal and was probably due to a terminal acidosis. The results are recorded in Tables 1 and 2. There was no evidence that irradiation lowered the alkali reserve, whether vomiting occurred or not. Table 3 gives the observations made at intervals on the plasma carbon dioxid content of Dog 3, the control animal.

To determine whether or not even a slight reduction in the alkali reserve occurred during the hours following irradiation, a supplementary experiment was run with Dog 3 as the subject. With the animal fasting, four control observations on the plasma carbon dioxid content were made at intervals on March 1, 1922, and one on the morning of March 2. As shown in Table 4, there was a slight fall which

6. Gauss, H.: The Effect of Morphin on the Alkali Reserve of the Blood of Man and Certain Animals, J. Pharmacol. & Exper. Therap. **16**:475, 1920.

7. Chanutin, A.: Animal Calorimetry—The Influence of the Ingestion of Meat and of Glycine and Alanine on the Carbon Dioxid Combining Power of Blood Plasma, J. Biol. Chem. **49**:485, 1921.

TABLE 1.—Observations on the Plasma Carbon Dioxid Content of Dog 1 After Irradiation

Date	Quantity of Radiation*	Reaction	Bled After Irradiation, Hours	Plasma CO_2 Content, Vol. per Cent.	Weight in Kilos
10/10/21	0	.....	.....	53.8	
10/13/21	0	.....	.....	61.9	12.0
10/17/21	50	Vomited	Not bled		
10/25/21	50	Vomited	18	65.6	
10/31/21	50	Vomited	6	47.8	
11/ 7/21	50	Vomited	3	52.5	
11/14/21	75	Vomited	3½	49.4	
11/21/21	75	Vomited	2	49.2	
11/28/21	75	Vomited	4	58.9	
12/ 5/21	75	Vomited	3	49.6	
12/12/21	75	None	2½	64.6	10.3
12/19/21	40	None	2½	67.9	
12/26/21	0	.....	.....	55.4	9.0
1/ 2/22	50	None	2	58.4	
1/ 9/22	40	None	3	49.5	7.5
1/18/22	0	.....	Bled just before etherization	36.4†	6.4

* In milliampere-minutes with a target-skin distance of 8 inches, a spark gap of 9 inches (between spheres) and a filter of 5 mm. of aluminum. The radiation was applied either over the upper abdomen or over the back in such a way that the viscera of the upper two-thirds of the abdomen were involved each time.

† Only at the last observation was the plasma carbon dioxid content reduced below the normal. As this was made nine days after the last irradiation when the animal was extremely weak, it was thought to be a terminal acidosis, not related directly to the irradiation.

TABLE 2.—Observations on the Plasma Carbon Dioxid Content of Dog 2 After Irradiation

Date	Quantity of Radiation*	Reaction	Bled After Irradiation, Hours	Plasma CO_2 Content, Vol. per Cent.†	Weight in Kilos
10/10/21	0	.....	.....	47.2	
10/14/21	0	.....	.....	48.3	10.3
10/17/21	50	None	Not bled		
10/25/21	50	None	16	50.2	
11/ 1/21	50	None	6	50.0	
11/ 8/21	60	None	3	47.3	
11/15/21	75	Vomited	2½	48.3	
11/22/21	75	Vomited	2	49.5	
11/29/21	75	Vomited	4	46.6	
12/ 6/21	75	None	Not bled		
12/13/21	60	None	3	52.0	9.8
12/20/21	0	.....	.....	47.3	
12/27/21	50	None	3	46.4	8.0
1/ 3/22	50	None	2½	57.1	
1/11/22	35	None	2	49.4	6.6

* In milliampere-minutes as described under Table 1.

† No reduction of the plasma carbon dioxid content below the normal was found.

TABLE 3.—Observations on the Plasma Carbon Dioxid Content of Dog 3*

Date	Plasma CO_2 Content, Vol. per Cent.	Weight in Kilos
10/11/21	53.4	
10/17/21	44.8	11.0
12/16/21	52.0	11.7
12/23/21	51.6	
12/30/21	51.9	12.1
1/ 6/22	51.5	

* This animal was not irradiated during this period. He was kept as a control under the same conditions as the other two.

possibly was related to the fast. On the morning of March 8, the fasting animal was given an irradiation of 75 ma. minutes with the setting described above. He was bled at intervals of approximately two hours during the day and once the following morning, the first bleeding being made about an hour and a quarter after irradiation when he was showing evidences of nausea. One and three-quarters, three and one-half and four and one-half hours after irradiation he vomited a colorless watery material containing no free hydrochloric acid. During this period he was noticeably inactive. About six hours after the treatment he became more lively and in a short time he appeared to be quite normal. The experiment was repeated April 3 with practically the same

TABLE 4.—OBSERVATIONS ON THE PLASMA CARBON DIOXID CONTENT OF DOG 3 MADE AT INTERVALS AFTER IRRADIATION *

Date	Time of Bleeding	Plasma CO_2 Content, Vol. per Cent.	Weight in Kilos	Remarks
3/1/22	9:50 a.m.	52.0	11.1	Animal fasting; no roentgen ray
	11:50 a.m.	48.3		
	2:15 p.m.	49.1		
	3:45 p.m.	48.3		
3/2/22	9:30 a.m.	46.2		
3/8/22	9:15 a.m.	49.6	....	Animal fasting; roentgen ray, 75 ma.-min. over abdomen ending 7:55 a.m.; vomited watery material at 9:35, 11:30 and 12:30; vomitus contained no free H Cl
	11:10 a.m.	56.4		
	1:20 p.m.	54.9		
	3:30 p.m.	50.8		
	5:05 p.m.	49.0		
3/9/22	9:15 a.m.	51.8		
4/3/22	9:15 a.m.	53.5	10.5	Animal fasting; roentgen ray, 75 ma.-min., over abdomen ending 8:15 a.m.; vomited watery material at 9:30, 11:00 and 12:30; free H Cl present in specimen at 9:30 a.m.
	11:10 a.m.	56.7		
	1:20 p.m.	56.5		
	3:05 p.m.	50.6		
	5:05 p.m.	52.7		
4/4/22	9:15 a.m.	52.5		

* The setting for the irradiation was as described under Table 1. The figures show a slight rise instead of a fall in the plasma carbon dioxid content during the first few hours after irradiation.

result, except that the first vomitus contained free hydrochloric acid. It will be seen in Table 4 that, on both occasions, the plasma carbon dioxid content, instead of diminishing during the reaction, rose slightly and then fell slightly below the first figure.

Aside from the question of the alkali reserve, it may be of interest to record other facts observed during the experiments. Epilation of hair with desquamation of the skin over the irradiated areas appeared about four weeks after the first application of the rays, but no definite erythema or destruction of the skin occurred. The first three or four irradiations seemed to cause the animals slight transient discomfort in spite of the vomiting. After that they began to show lack of energy and to refuse food for two or even three days. About the sixth week it became evident that both dogs were losing weight. From that time

on, as the weights recorded in the tables show, the loss was increasingly rapid. Dog 1 lost altogether 5.6 kilos, or 46 per cent., of his weight, and Dog 2 lost 3.7 kilos, or 37 per cent. During this period the control dog gained 1.1 kilos. The emaciation was so extreme and developed so rapidly during the last month of the experiment that it does not seem reasonable to attribute it alone to the periods when the dogs refused food, although this must have been a factor. During the last month of the experiment both animals frequently passed loose and at times watery stools, occasionally containing streaks or flecks of blood.

Although Dog 2, a young animal, reacted less than the older one, as far as vomiting was concerned, he showed more evidence of weakness and prolonged anorexia. He was found dead on the morning of Jan. 15, 1922. Unfortunately, I was away from the laboratory and was not notified until two days later, the body being kept meanwhile in the refrigerator. At necropsy, nothing definitely abnormal was found except a perforation of the anterior wall of the stomach which was interpreted as a postmortem change. This interpretation was confirmed by the fact that no evidence of an inflammatory reaction in the margin of the perforation was found on histologic examination. No areas of ulceration or necrosis were seen in the intestinal tract.

Dog 1 vomited more consistently after irradiation but seemed to maintain his strength better and to recover his appetite sooner than the younger animal. January 18 his respirations were deep and slow, quite suggestive of the hyperpnea seen in clinical acidosis. As it did not appear likely that he would live more than a few hours, he was bled and then etherized and a necropsy was performed immediately. The plasma carbon dioxid content was 36.4 volumes per cent., undoubtedly indicating a diminished alkali reserve. In view of the fact that the dog had not been irradiated for nine days, this acidosis was thought to be a terminal thing and not related to "treatment sickness." At necropsy, this animal showed nothing definitely abnormal grossly aside from extreme emaciation. The stomach contained considerable undigested meat. The colon contained semifluid yellow feces which in the rectum were blood tinged. No hemorrhagic areas, ulceration or other evidence of destruction of epithelium were found anywhere in the gastro-intestinal tract, as have been described in rabbits by Denis, Martin and Aldrich [8] and in dogs by Hall and Whipple [8] and Warren and Whipple,[9] following a single dose of roentgen rays large enough to kill the animal.

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8. Hall, C. C., and Whipple, G. W.: Roentgen Ray Intoxication, Am. J. M. Sc. **157**:453, 1919.

9. Warren, S. L., and Whipple, G. W.: Roentgen Ray Intoxication. I. Unit Dose Over Thorax Negative—Over Abdomen Lethal. Epithelium of Small Intestine Sensitive to Roentgen Rays. II. A Study of the Sequence of Clinical, Anatomic and Histologic Changes following a Unit Dose of Roentgen Rays, J. Exper. Med. **35**:187, 1922.

Dog 3, which had been given 75 ma. minutes over the abdomen March 8 and April 3, was etherized and a necropsy performed April 4, thirty hours after the second irradiation and about twenty-four hours after he showed signs of recovery from the resulting reaction. The necropsy showed nothing abnormal in the gross.

Microscopic examination of the liver, pancreas, kidney, suprarenal and celiac ganglion of Dog 1 discloses nothing abnormal. No evidence of an endarteritis is seen in any of the sections. Of the parts of the gastro-intestinal tract, the stomach shows the most marked changes. There is a definite increase in the fibrous tissue of the stroma of the mucosa. In many places the gastric glands do not extend to the muscularis mucosae. The gastric tubules in some areas are replaced by fibrous tissue and in other places all that remains of a tubule is three or four of the deeply acid-staining parietal cells completely surrounded by what seems to be young fibrous tissue. Whatever the damaging mechanism may have been—the rays themselves directly or stimulation of fibrous tissue indirectly—the parietal cells seem to have been distinctly more resistant than the chief cells. The columnar epithelial cells of the surface and pits show no evidence of damage. The lymphoid cell content of the solitary nodules has been markedly reduced. In the small intestine the columnar epithelial cells appear normal. Cells of the lymphoid series are greatly diminished in number in the tips of the villi and in many instances are absent. The nodules of lymphoid tissue in the tunica propria show evidences of destruction, invasion by fibroblasts and endothelial cells and regeneration of germinal centers. The large intestine shows nothing definitely abnormal. A section of a mesenteric lymph node shows very rare lymphoid cells, except around the periphery, where new germinal centers have formed, the cells in which show many mitotic figures and from which lymphoid tissue is invading the node in chords. The reticular tissue is infiltrated with large numbers of polymorphonuclear leukocytes and endothelial cells. The latter are manifesting great phagocytic activity, some of them containing as many as four polymorphonuclear cells. The splenic nodules are reduced in number and size and there is a marked diminution in the number of lymphoid cells in the pulp of the spleen.

Because of postmortem changes, sections from the tissues of Dog 2 are unsatisfactory. However, they disclose nothing contradictory to the findings in the tissues of Dog 1.

Sections of the liver, pancreas, suprarenal, celiac ganglion, stomach and large intestine of Dog 3 show nothing definitely abnormal. In the villi of the small intestine the lymphoid cells are somewhat reduced in number. An abdominal lymph node shows changes similar to those seen in the node of Dog 1 but to a much less extent. The splenic nodules are small. In the center of some of them there is a reaction

consisting of clusters of large mononuclear cells with clear nuclei and pale staining cytoplasm, some of which are phagocytic. The splenic pulp contains large numbers of migrating leukocytes and a reduced number of lymphoid cells.

Observations on the plasma carbon dioxid combining power of two patients undergoing roentgen-ray treatment in the wards of the Peter Bent Brigham Hospital are recorded in Table 5. From 250 to 300 ma.

TABLE 5.—OBSERVATIONS ON THE PLASMA CARBON DIOXID COMBINING POWER OF TWO PATIENTS RECEIVING ROENTGEN-RAY TREATMENT

Patient, Med. No., Diagnosis	Date	Area Irradiated*	Reaction After Irradiation	Time of Bleeding in Relation to Treatment	Plasma CO_2 Combining Power, Vol. %
W. J. 16741 Carcinoma of prostate	9/24/21	.....	.....	Before	62.4
	9/24/21	Lower abdomen	Nausea, repeated vomiting, exacerbation of pain	6 hrs. after	61.7
	10/13/21	Lower abdomen	Slight anorexia, no nausea	22 hrs. after	62.9
	11/ 2/21	Lower abdomen	Repeated vomiting, diarrhea, pain all over	5 hrs. after	61.1
M. R. 16948 Carcinoma of ovary with ascites	10/20/21	.....	.....	Before	65.0
	11/ 5/21	Lumbar region	Slight nausea, vomited once	3 hrs. after	63.8
	11/23/21	Lower abdomen	Nausea, vomited three times	2 hrs. after	60.4
	4/ 3/22	.....	.....	2 mo. after last treatment	52.8
	4/ 4/22	Lower abdomen	Nausea, repeated vomiting, reaction began before treatment was finished	3½ hrs. after	55.4

* These patients were treated by Dr. Lawrence Reynolds and received from 250 to 300 milliampere-minutes from a broad focus Coolidge tube activated by a Victor-Snook interrupterless transformer with a spark gap of 9 inches between spheres, a target-skin distance of 12 inches and a filter of 0.5 mm. of copper.

minutes were given, using a spark gap of 9 inches between spheres, a target-skin distance of 12 inches and a filter of 0.5 mm. of copper. A few hours after the irradiation, during the reaction, blood was taken from an arm vein with a syringe and put into a tube containing a crystal of potassium oxalate. After centrifuging, the plasma was equilibrated with normal alveolar air and the carbon dioxid determined by Van Slyke's method (1917). No evidence of acidosis was found.

CONCLUSION

No evidence that the constitutional reaction following irradiation with roentgen ray is associated with a lowered alkali reserve was found in several determinations of the plasma carbon dioxid combining power of four patients and in repeated determinations of the plasma carbon dioxid content of three dogs.

I wish to thank Dr. Lawrence Reynolds, roentgenologist to the Peter Bent Brigham Hospital, for the use of roentgen-ray apparatus and to express my appreciation of the cordial cooperation of Prof. S. Burt Wolbach in checking up the pathologic findings and of Dr. G. H. Hansmann, resident pathologist, in the preparation of the pathologic material.

AN ANALYSIS OF SOME OF THE FACTORS OF VARIABILITY IN THE VITAL CAPACITY MEASUREMENTS OF CHILDREN *

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The use of vital capacity measurements of the lungs in a comparative way implies a certain standard of reliability of the measurements on the normal subject. If the observations made on the normals cover a wide range of variability, then small differences, such as may well arise from moderate disturbances in function, will be obscured, and the practical value of the test greatly diminished.

In adults the limitations and practical usefulness of vital capacity measurements have been clearly shown in the work of Peabody,[1] West[2] and others. More recently, we have applied the test to children and have indicated a line of usefulness in this field.[3] A question concerning the reliability of the results naturally arises, however, when vital capacity measurements are made on young subjects, since there are two outstanding ways in which the test, as applied to children, may be expected to yield more variable results than when applied to adults. First, the satisfactory performance of the test depends in large measure on an immediate and complete forcing-out of the air from the lungs when the test is made, and young subjects present some difficulty in getting a thorough expulsion of the air; and second, it is necessary to relate vital capacity to some other body measurement, such as height, weight, or body surface area, and during the growing period these body measurements are subject to marked change and individual differences.

The present study is an attempt to determine to what extent different methods of measuring the vital capacity influence the final values, and to define in a statistical way the amount of variability exhibited in a large series of vital capacity observations on children who were selected only with respect to the age limits of from 6 to 16 years and to clinically normal subjects.

Methods of Measuring the Vital Capacity.—In a previous paper[3] dealing with the vital capacity of children with heart disease we have given a figure representing the mean value obtained on a group of

* From the Departments of Physiology and Pediatrics, Cornell University Medical College.

1. Peabody, F. W., and Wentworth, J. A.: Arch. Int. Med. **20**:443 (Oct.) 1917.
2. West, H. F.: Arch. Int. Med. **25**:306 (March) 1920.
3. Wilson, M. G., and Edwards, D. J.: Am. J. Dis. Child. **22**:443 (Nov.) 1921.

normal subjects. While this work was in print, Emerson and Green [4] reported observations on the vital capacity of normal children of about the same age range that are significantly lower than those obtained by us. We have, therefore, studied the matter further in an attempt to discover some of the reasons for the apparent difference in the two sets of observations. Our observations were made with a specially constructed spirometer of the Gad-Krogh type. In the calibration of this instrument the water displacement method was first used to measure off the liter divisions, and then the entire scale was checked against a ten liter Bohr meter. A recalibration of the instrument has recently been made and this was found to confirm the original values. We believe, therefore, that errors in calibration can be excluded as a possible cause for the higher values obtained by us.

A second method of checking our results has been to compare the readings obtained with our instrument with those obtained on the same subjects with other spirometers. Thirty-six subjects, ranging in size from 0.83 to 1.54 sq. m. surface area, were selected for the first series in the test. The measurements of the vital capacity were taken on each subject with three spirometers and with only a few minutes intervening between each set of observations. The instruments used beside our own were the Sanborn, made by the Sanborn Company, of Boston, and the Standard, made by the Narragansett Machine Company, of Providence. The Standard instrument was calibrated by the same method as that described above and a corrected scale placed upon it.

The Sanborn instrument gave results that agree very closely with those obtained with our instrument. The average figure for the series shows a difference of a little less than 1.5 per cent., with the Krogh instrument giving the higher values. When the results are arranged into groups on the basis of the surface area of the subjects there is shown a remarkable parallelism of the values obtained with these instruments throughout the size range. With the Standard spirometer the results show consistently lower readings amounting to a difference of a little more than 10 per cent. for the averages of the group, when compared with the figure obtained with our instrument. There is also greater variation from group to group than is exhibited in the results with the other instruments.

In another series of 115 cases we have compared the results obtained with other Standard spirometers (not calibrated by us) with those obtained with the Sanborn. It should be noted, however, that the measurements in this series with the Standard instruments were not taken at the same sitting, but at a previous time ranging from a few

4. Emerson, P. W., and Green, H.: Am. J. Dis. Child. **22**:202 (Sept.) 1921.

days to as much as a month. It will not be possible, therefore, to relate these values in a quantitative way. The significant feature in these results is the greater variability in the group averages given from the measurements with the Standard spirometer over those obtained on the same subjects with the Sanborn instrument.

Another series of tests has been made, similar in procedure to the above, to compare the measurements obtained with a Dry spirometer made by Thomas Upham, of Boston, with those obtained with the Sanborn. Forty-one subjects were included in this series, and the average values for the group exhibit lower readings with the Dry spirometer by about 11.6 per cent. We are not justified in placing very much stress on this quantitative difference, since the measurements were not taken on the same date. But observations covering much longer intervals make it evident to us that the lower reading with the Dry spirometer cannot be explained on the basis of time changes.

It is indicated from these results that certain types of spirometers tend to give lower readings than others and that the group values obtained with the low reading spirometers generally exhibit greater variability. Differences of this character result in no small degree, we believe, from the use of instruments not sufficiently sensitive for the measurement of the vital capacity of children.

Another factor that appears to account for part of the discrepancy between the observations reported by Emerson and Green and those we have obtained is in the different method used for estimating the surface area. They employed, for the most part, the Benedict-Talbot method, whereas we have used exclusively the DuBois height-weight method. In order to obtain some notion of the extent of influence which this difference in the method of estimating the surface area might have on the final results, we selected at random ten cases published in the tables by Emerson and Green and have calculated these on the basis of the DuBois surface area chart. The results show an average about 12 per cent. higher than their figures for the same subjects.

These considerations, while indicating two factors which make for the lower vital capacity values reported by Emerson and Green, do not account for the comparatively large difference between their findings and those we have obtained. If more complete data were available concerning technic and character of the subjects, it might suggest other factors that have contributed to the discrepancy, but in the absence of such material it is of no avail to speculate.

Variation of the Vital Capacity in a Group of Normal Subjects.—In a group of thirty-five children in whom stem length, chest circumference, height, weight and vital capacity were taken we found[3] that

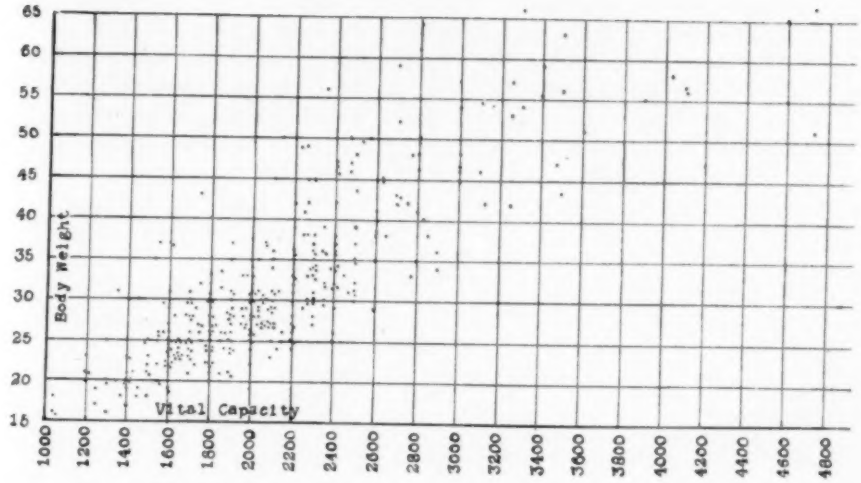

Chart 1.—Body weight (kg.) against vital capacity (c.c.).

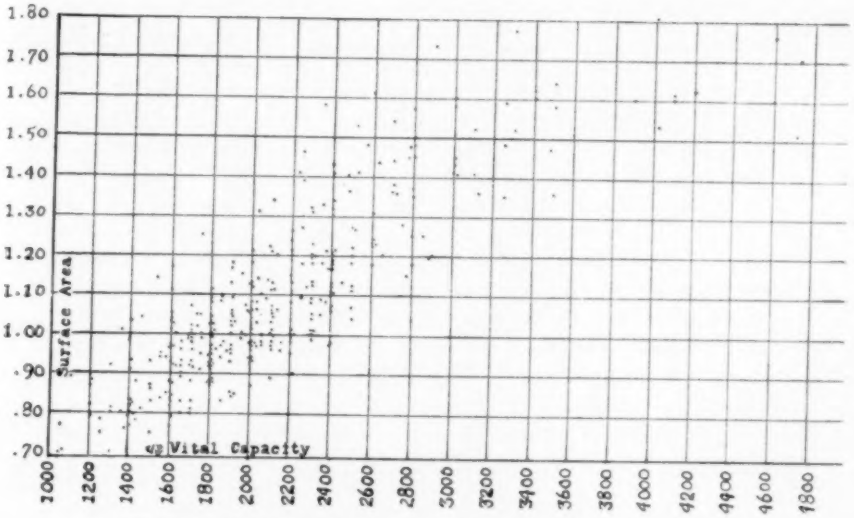

Chart 2.—Surface area (sq. m.) against vital capacity (c.c.).

in using Dreyer's [5] standards for vital capacity the correlation to the surface area measurement (surface area calculated from the DuBois height-weight chart) appeared to be as close as that to any of the other body measurements. On the basis of this and also the work of West [2] and of Dreyer [6] on adults, the suface area unit was adopted for relating all our vital capacity measurements. The work has been extended so that we now have records of the vital capacity, height and weight of 360 clinically normal children. This amount of material has seemed to warrant a closer study of the degree of variation exhibited, with a view to a more exact evaluation of its significance and better methods of expressing the results.

At present there is, in general, no better way of gaining a clear impression of the degree of variability of a series of observations

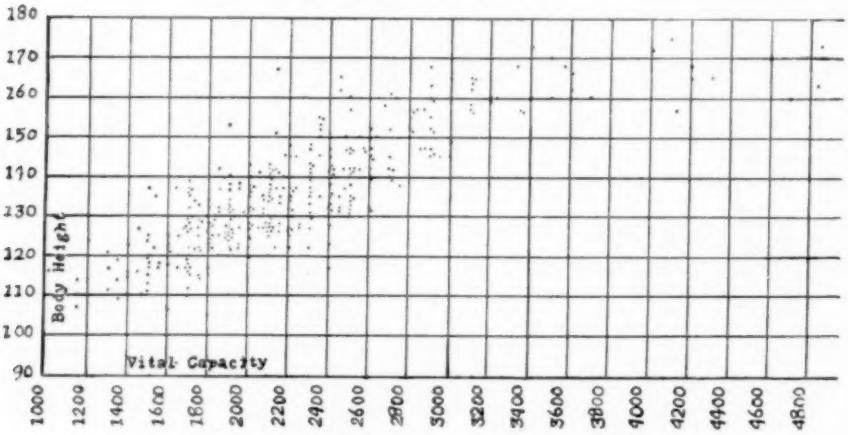

Chart 3.—Body height (cm.) against vital capacity (c.c.).

than to arrange them in the form of a plot. Although somewhat more time consuming, this method has the advantage of showing at a glance in which part of the range of variables there is present the greatest degree of scatter. In the present analysis the data have been arranged to plot the vital capacity as related to weight, to height and to body surface area.

An examination of these plots, shown in Charts 1, 2 and 3, reveals the greatest degree of scatter when the body weight is taken as the

5. Dreyer, G., in collaboration with G. F. Hanson: The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body, with Tables, Cassell and Company, London, New York, Toronto and Melbourne, 1920.

6. Dreyer, G.: Lancet **1**:197, 227, 1919.

measure of relationship; also that there is little difference between relating the vital capacity to surface area and that relating it to height alone. In the weight relation the greatest amount of scatter is shown by the measurements taken on the larger subjects. This we interpret to mean that the factors which make for variability in weight are operative to a greater extent in children weighing more than 40 kg.

The plot for the height relation shows a fairly well grouped set of observation throughout the range. The method of relating the vital capacity to surface area presents a close correlation in that part comprising the smaller subjects, but, like the weight relation, shows divergence as we approach the higher vital capacity readings from larger subjects. This feature of the surface area relation naturally follows from relations previously shown for the height alone and for the weight alone, since the method of deriving surface area contains an element of both factors.

In the light of these results, the method of relating the vital capacity to a body height measurement seems indicated as a general practical procedure. This does not imply that the vital capacity measurement in children is more closely correlated to body height than it is to surface area as we have derived the latter, but it is interpreted rather to indicate that the inherent errors in the weight measurement, when deductions have to be made for clothing, and the accumulative errors, when surface area calculations are carried out from these measurements, more than offset the slight difference in absolute correlation which the surface area relation may contain.

In turning now to the problem of the closeness of correlation of the vital capacity to the surface area it will be important to remember that our subjects present a normal group from an ordinary clinical standpoint. Beyond this it is impossible to speak with exactitude in regard to their soundness; in fact, in the light of more recent work, there is reason for believing that a small percentage of the group would reveal abnormal conditions with more exact methods of diagnosis. It is of interest to note, therefore, that the standard deviation of this series, which gives a measure of the variability in terms of the unit in which the variable is measured, i. e., in liters vital capacity per square meter body surface area, is 0.272 for the 360 cases. To obtain a measure in relative terms of the variability of different characteristics measured, it is customary to express them as percentages of their individual means. This coefficient of variation (C. of V. $= \frac{100\,\sigma}{\text{mean}}$) in the present series is found to be 14.2 per cent.

In variability, as measured in the absolute terms of the standard deviation and in the derived relative term of the coefficient of variation, our series shows a value slightly greater in magnitude than certain

other physiological measurements, such as the pulse rate and the heat production in adults,[7] but it is less than that reported on such measurements as keenness of sight [8] and heat production in infants.[7]

The results of this brief comparison indicate that our series shows a satisfactory agreement with the results of others on fairly comparable physiological measurements. The agreement seems rather remarkable when one considers the probable influence of age, sex, race, the small percentage of cases not strictly normal, and the differences in mental cooperation in the test.

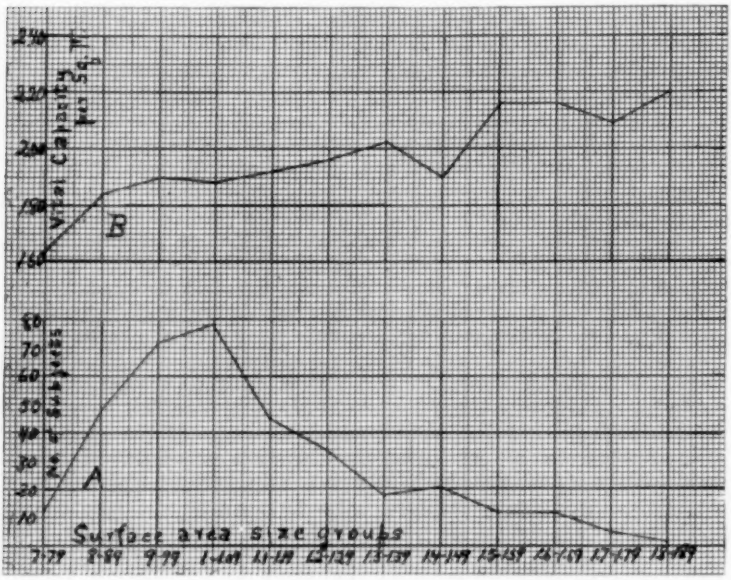

Chart 4.—(A) Distribution of subjects grouped according to surface area size. (B) Average vital capacity of each group in surface area size arrangement.

Vital Capacity as Related to Body Size.—In the course of these observations on the vital capacity of children, as related to surface area, we have been impressed by the frequency with which low readings were obtained on small children, and similarly a tendency for larger subjects to give higher readings.

The surface area measurement, containing as it does a height and weight element, probably expresses more exactly than any other body

7. Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington, Pub. 279, 1919.

8. Pearson, K.: The Chances of Death and Other Studies in Evolution, E. Arnold, London, 1897.

measurement the body size relation of groups of subjects differing markedly in their individual proportions. On the basis of this conception of body size, we have divided the whole range of our 360 cases into groups of convenient units as regards their surface area size. Each subject was then assigned to the appropriate group with his vital capacity calculated on the basis of his surface area. The mean value for each group was then determined with a view of showing to what extent size introduces a variable in a statistical average for the whole series.

The results of this method of analysis are very well brought out in Chart 4. The curve at the bottom (A) shows the frequency distribution in terms of the group totals. It exhibits a skew type of curve with the mode at about 1 sq. m. surface area size. This form of the curve merely signifies that, in selecting our subjects from the ages of six to sixteen, inclusive, we have inadvertently obtained a preponderance of subjects in the lower half of the range. The upper curve (B) of the mean vital capacity for each size group shows a distinctly upward trend from the smaller to the larger sized subjects. The slope of the curve suggests that, with a larger number of cases, it would give a straight line cutting approximately the point 1.74 at the lower, and 2.18 at the higher range. This would give roughly a 25.2 per cent. range, which is probably statistically significant. It indicates that in the evaluation of an individual vital capacity measurement on the basis of surface area some account has to be taken of the actual size of the subject measured before an accurate estimate of the deviation from the normal can be made. It follows, therefore, that a single mean value derived from a large group of widely differing sizes of children offers only an approximation to the true mean of any individual class.

It is of interest in this connection to consider the possible meaning of the type of curve presented by this method of grouping according to body size. There is suggested the operation of at least three factors, either separately or in common: First, the method of deriving surface area may contain an element of inaccuracy with diminishing stature; second, the method of measuring the vital capacity may similarly introduce a constantly increasing error with smaller subjects; and third, the vital capacity in terms of its absolute relation to body size may undergo an increase in children as they approach maturity. The data at hand afford no basis for determining the degree of operation of these different factors.

It is pertinent to this discussion to note that in the grouping of the subjects according to the surface area size there is naturally a certain amount of segregation of age relations. The subjects comprised, for example, in the group from 0.7 to 0.79 sq. m. surface area,

are as a group younger than those included in the group from 1.20 to 1.29 sq. m. An analysis of these group results will show, therefore, whether less variability goes with greater maturity and stature. If we use as a measure of variability the coefficient of variation, it is evident from the accompanying table that the small young subjects do not give values significantly more variable than shown by the older and larger subjects.

THE VARIABILITY OF THE VITAL CAPACITY MEASUREMENTS SHOWN BY DIFFERENT GROUPS ARRANGED ACCORDING TO SURFACE AREA SIZE

Group	No. of Cases	Maximum	Minimum	Percentage Range	Mean	Standard Deviation	Coefficient of Variation
0.7-0.79	12	2.97	1.28	61.8	1.64	0.233	14.2
0.8-0.89	49	2.35	1.37	71.5	1.84	0.252	13.9
0.9-0.99	72	2.44	1.42	71.8	1.90	0.220	11.6
1.0-1.09	79	2.34	1.33	76.0	1.89	0.237	12.5
1.1-1.19	45	2.38	1.33	79.0	1.92	0.232	12.1
1.2-1.29	34	2.30	1.41	63.0	1.96	0.234	11.9
1.3-1.39	18	3.10	1.41	120.0	2.02	0.260	12.9
1.4-1.49	22	2.36	1.54	53.0	1.90	0.203	10.7
1.5-1.59	12	3.23	1.48	118.0	2.18	0.350	16.0
1.6-1.69	12	2.88	1.52	89.5	2.18	0.500	22.9
1.7-1.79	5	2.77	1.57	76.5	2.09	0.248	11.9

These results support the conclusion that the observations made on small young children are statistically as reliable as those obtained from the more mature subjects; moreover, they indicate that the lower mean values shown in the curve of Chart 4 for the subjects of small surface area size are probably not due to an error inherent in the method, which is inversely related to size and age of the subjects measured.

SUMMARY

The measurement of the vital capacity of children with certain types of spirometers has given results 10 per cent. or more below that obtained on the same subjects with other instruments. Moreover, the results obtained with those instruments giving low readings exhibit a greater degree of variability. It is suggested that the low readings of a more fluctuating character are probably due to the use of a spirometer not sufficiently sensitive for the measurement of the vital capacity of children.

The vital capacity observations on 360 normal children, when related separately to the body measurements, height, weight and surface area, exhibit a correlation slightly to the advantage of the height relation. It is suggested that the height unit may be the most practical body measurement for the relating of the vital capacity of children; not that the absolute correlation is greater than the surface area unit, but rather that the chances for errors in the calculations are less and in practice will more than offset any fundamental difference there may be in favor of the surface area method.

The absolute variability in this series, as shown by the standard deviation, is 0.272 liters per square meter surface area. The coefficient of variation is shown to be 14.2 per cent., a value agreeing fairly well with that of other physiological variables of a comparable nature.

Based on the surface area measurement as a criterion of body size, certain groupings have been made. The mean vital capacity of each of these groups was obtained, and from these data it has been shown that the vital capacity, as related to a unit of surface area, exhibits gradually increasing values from the smaller to the larger-sized subjects. This difference is estimated to be of the order of a 25 per cent. range for the size groups.

In terms of the coefficient of variation, the groups comprising the smaller surface area size, which were likewise made up of younger subjects, do not exhibit greater variability than the groups of larger surface area size made up of older subjects. It is argued that the age factor does not make for greater variability in the measurement of the vital capacity of children.

CONCLUSIONS

1. A spirometer that offers minimal resistance to the egress of the air from the lungs is necessary for measuring the vital capacity of children.

2. The correlation between vital capacity and body height is more intimate than that between vital capacity and surface area, or body weight.

3. The vital capacity values obtained from children show a degree of variability about equal to that exhibited by other fairly comparable physiologic variables. Young children give results that are not more variable than those from older ones.

4. Children of small stature exhibit a lower vital capacity per unit of surface area than those of larger stature.

STUDIES ON THE RESPIRATORY ORGANS IN HEALTH AND DISEASE

VI. THE SIGNIFICANCE OF THE VITAL CAPACITY TEST IN PULMONARY TUBERCULOSIS, BRONCHIAL ASTHMA, PNEUMONIA AND AN ACUTE INFECTION OUTSIDE THE RESPIRATORY TRACT *

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In the last decade, particularly the latter half of this decade, the vital capacity test, together with certain measurements of the body from which physical fitness is ascertained, has rapidly been gaining in favor with physicians especially interested in diseases of the heart and lungs. The present study of which this paper is only a preliminary report represents an attempt to investigate carefully the value of the vital capacity test in diseases of the lungs.

Recently I reported [1] approximately 100 cases in all of which stereoroentgenograms were made. Later [2] I reported 230 cases. Since these papers were prepared further data have been collected and compiled on cases of pulmonary tuberculosis, bronchial asthma, pneumonia and one acute infection outside the respiratory tract (paratyphoid fever).

I. PULMONARY TUBERCULOSIS

The present report details the findings in 335 cases. Unfortunately roentgenograms could be had in only 210 cases. In all other cases the remaining necessary aids in diagnosis were employed and there was finally no doubt as to the diagnosis in any case.

Table 1 shows that on a basis of the roentgen-ray examination the cases were classed as follows: I. Suspected cases: *A*. Roentgen-ray examination negative. II. Tuberculous cases: *A*. Peribronchial tuberculosis, (1) unilateral; (2) bilateral. *B*. Parenchymatous tuberculosis, (1) unilateral (*a*) disease confined above the first rib or an area of similar size; (*b*) disease extending below the first rib, but not involving more than one lobe; (*c*) involvement of more than one lobe;

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* From the Department of Internal Medicine, University of Minnesota, and the Tuberculosis Department of the Minneapolis General Hospital.

* Read in part before the ninth session of the Mississippi Valley Conference on Tuberculosis, Columbus, Ohio, Sept. 12-14, 1921.

1. Myers, J. A.: IV. A Comparison of Vital Capacity Readings and Roentgen-Ray Findings in Pulmonary Tuberculosis, Tr. National Tuberculosis Association, New York, June, 1921, A. Rev. Tuberc. **5**, 1922.

2. Myers, J. A.: V. A Comparison of Vital Capacity Readings and Physical Signs in Pulmonary Tuberculosis, Minnesota Med. **5**:233 (April) 1922.

(2) bilateral (*a*) disease confined above the first rib or an area of similar size on each side; (*b*) disease extending below the first rib on each side but not involving more than two lobes; (*c*) involvement of more than two lobes.

There are thirty suspected cases in which the roentgenograms showed no evidence of disease. The mean vital capacity percentage for this group is 102, while the range is between 82 and 122 per cent.

The group in which roentgenograms revealed unilateral peribronchial tuberculosis consists of thirty-one cases. The average vital capacity for this group is 96 per cent. and the range is from 81 to 121 per cent. There are only eight cases of bilateral peribronchial tuberculosis in the group and their mean vital capacity percentage is 102, while the range is between 87 to 112 per cent.

Thirty-three cases showed unilateral parenchymatous tuberculosis above the first rib or a single area of similar size in some other part

TABLE 1.—CLASSIFICATION OF CASES ON BASIS OF ROENTGEN-RAY EXAMINATION

	Number of Cases	Vital Capacity Percentage		
		Average	Lowest	Highest
I. Suspected cases				
A. Roentgen-ray negative	30	102	82	122
II. Tuberculous cases				
A. Peribronchial tuberculosis				
1. Unilateral	31	96	81	121
2. Bilateral	8	102	87	112
B. Parenchymatous tuberculosis				
1. Unilateral				
(a) Above first rib	33	96	74	119
(b) No more than one lobe involved	23	87	31	122
(c) More than one lobe involved	15	65	38	106
2. Bilateral				
(a) Above first rib	15	86	51	108
(b) No more than two lobes involved	30	73	43	119
(c) More than two lobes involved	25	54	26	82

of the lung. The average vital capacity for this group is 96 per cent., but the range is between 74 and 119 per cent. There is a group of twenty-three cases with more extensive disease than the last group mentioned but in no case does the involvement extend over more than one lobe. This group shows an average vital capacity of 87 per cent. with a range of from 31 to 122 per cent. There are only fifteen cases in the group in which the roentgenograms show unilateral disease involving more than one lobe. The average vital capacity for this group is 65 per cent., while the range is from 38 to 106 per cent.

The group of fifteen cases in which the roentgenograms show disease limited to that part of each lung above the first rib or an area of similar size on each side presented an average vital capacity of 86 per cent. with a range of from 51 to 108 per cent. In the next group, which consists of thirty cases with involvement limited to one lobe on each side, the average vital capacity is 73 per cent., while the range is from 43 to 119 per cent. It is not surprising to find that

the last group, consisting of twenty-five cases with disease involving more than two lobes, presents the lowest vital capacity percentage. The average for this group is 54 per cent., while the range is from 26 to 82 per cent.

On the basis of the physical examination, the patients were grouped as follows: I. Suspected cases (*a*), no physical signs; (*b*) physical signs indefinite (diagnosis reserved). II. Definitely tuberculous cases, (*a*) minimal disease; (*b*) moderately advanced disease; (*c*) far advanced

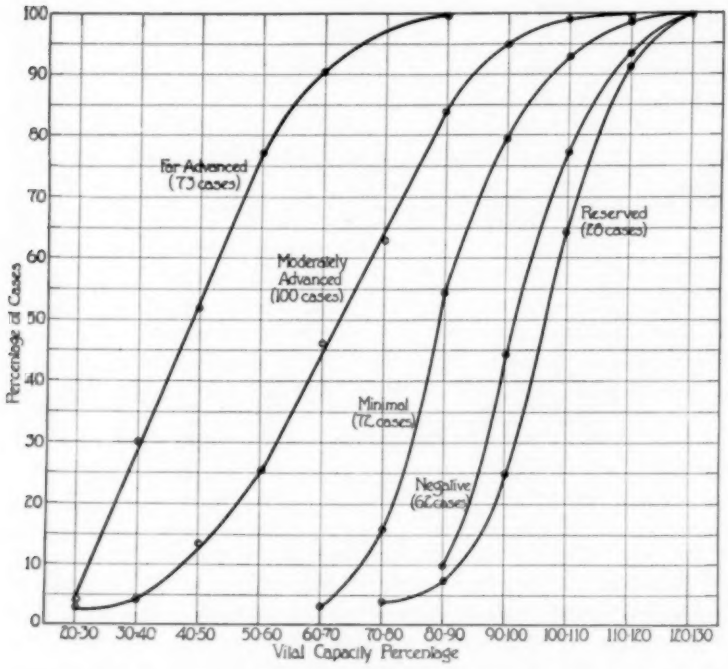

Fig. 1.—Ogive curves showing percentage of cases in each stage plotted against the percentage of vital capacity.

disease. Ogive curves (Fig. 1) were made in order to facilitate in the visualization and analysis of the data in each group of cases.

From these curves it will be seen that the range of vital capacity percentage is indicated in each group. For example, along the curve representing the far advanced cases we see within the from 20 to 30 per cent. vital capacity percentage line a small circle. This circle lies at a height representing approximately 4 per cent. of the cases studied. This means that approximately 4 per cent. of the far advanced cases

had vital capacities as low as 20 per cent. of the normal. If we pass upward along the curve we find another circle lying within the from 30 to 40 per cent. vital capacity percentage line and within the horizontal line representing 30 per cent. of the cases. Here we have added together all the cases with a vital capacity below 30 per cent. of the normal and it is obvious from the curve that approximately 30 per cent. of the far advanced cases have such reduced vital capacities. Such information may be obtained, all along the curve. The last circle at the upper end of the curve lies within the vertical line representing the from 80 to 90 per cent. vital capacity group. This circle also lies within the horizontal line representing 100 per cent. of the cases. It is, therefore, obvious that all of the far advanced cases have vital capacities below 90 per cent. of the normal.

From the use of these curves similar information may be obtained regarding the percentage of vital capacity in the moderately advanced, minimal, reserved and negative cases. One may ascertain quickly the vital capacity percentage of any given percentage of cases in all the

TABLE 2.—VITAL CAPACITY IN CASES OF THICKENED PLEURA, CAVITATION AND PNEUMOTHORAX

	Number of Cases	Vital Capacity Percentage		
		Average	Lowest	Highest
Cases with thickened pleura revealed by roentgen-ray examination	12	78	20	115
Cases with cavities revealed by roentgen-ray examination	30	64	31	109
Cases with pneumothorax	9	49	32	58

groups. If, for example, a horizontal line (a) is drawn representing 50 per cent. of the cases through all the curves it is seen that 50 per cent. of the far advanced cases have a vital capacity from 40 to 50 per cent. of the normal, while the remaining 50 per cent. have a higher vital capacity percentage. This horizontal line intersects the curve representing the moderately advanced cases slightly beyond the vertical line representing from 60 to 70 per cent. vital capacity, therefore, approximately 50 per cent. of the moderately advanced cases have vital capacities within or below from 60 to 70 per cent. of the normal. Further observation will show that approximately 50 per cent. of the minimal, negative and reserved cases have vital capacities within or below from 80 to 90, from 90 to 100 and from 100 to 110 per cent. of the normal, respectively.

In Table 2 the cases with thickened pleura revealed by roentgen-ray examination, cavitation revealed by roentgen-ray examination and pneumothorax (spontaneous and artificial) are grouped separately. There are only twelve cases in the group in which the roentgen ray revealed thickened pleura. Some of these cases have insignificant

pulmonary lesions while others have far advanced lesions of tuberculosis. The average vital capacity for the series is 78 per cent., while the range is from 30 to 115 per cent. It is interesting to note that in some cases with very slight pulmonary involvement the vital capacity is not at all or very slightly reduced. There are thirty cases in the group in which the roentgen-ray examination revealed pulmonary cavities. For this group the average vital capacity percentage is 64 while the range is from 31 to 109 per cent. The nine cases with pneumothorax show about what one might expect, that is, a reduction in vital capacity of approximately 50 per cent. The actual average for this group is 49 per cent., while the range is from 32 to 58 per cent.

The tables and curves show that those patients whose roentgenograms do not reveal disease have an average vital capacity of approximately 100 per cent. There are a few cases in this group with vital capacities slightly below normal. In most cases of this kind the reduction can be accounted for on the basis of such factors as age and obesity. There are several cases in this group with an overdeveloped vital capacity due to previous special training, hence their vital capacities are above 100 per cent.

The cases with peribronchial tuberculosis were found to have an average vital capacity which very nearly approaches 100 per cent. This average and the range of vital capacity does not differ much from the cases in which the roentgen ray did not reveal disease. It is interesting to note that those cases with bilateral peribronchial tuberculosis have an average vital capacity percentage which is higher than that of those cases with unilateral peribronchial tuberculosis.

In the thirty-three cases with parenchymatous lesions above the first rib on one side, the average vital capacity percentage is well within the normal limits. The low limit of the range in this group, however, is as low as 74 per cent. of the normal. From this small number of observations it appears that tuberculous lesions (although very small) of clinical significance reduce the vital capacity. On the other hand, there are several cases in this group with vital capacities above 100 per cent. It should be stated that in a few of these cases the roentgen-ray examination revealed only small areas of calcification or fibrosis. For example, in one case a fluoroscopic examination revealed a dark area about the size of a walnut in the region of one of the basal lobes. The examining physician being willing to make a diagnosis of early tuberculosis without the aid of stereoscopic plates and without a careful study of the symptoms sent this patient to a sanatorium for treatment. After admission to the sanatorium stereoscopic plates revealed evidence of a small area of calcification in one basal lobe. The remainder of both lungs was clear. This patient did not have one of the cardinal symptoms of tuberculosis and presented a vital capacity of 100 per cent.

Another patient whose stereoscopic plates now show evidence of a definite tuberculous infiltration was treated in a sanatorium three years ago. He has been working for the past two years and now, in spite of the roentgen-ray findings, has a vital capacity of more than 100 per cent.

In the group (Table 1) with more extensive unilateral disease, the average vital capacity percentage decreases; however, even in those cases with involvement of more than one lobe there is an occasional case with a vital capacity of 100 per cent. or more.

In the group of cases with bilateral disease there are fifteen with disease only above the first ribs. As might be expected, the average vital capacity percentage of this group is somewhat higher than in the group of unilateral cases with involvement of more than one lobe. Here, too, there are cases with only calcified or fibrous tuberculous processes limited to the extreme apices. Attention should be called to the fact, however, that while a few cases in this group have vital capacity percentages within normal limits, there are others with more severe disease with a vital capacity as low as 51 per cent. of the normal.

In the remaining groups of cases with bilateral disease the average vital capacity percentage decreases as the extent of involvement revealed by the roentgen-ray increases.

More than 100 ex-service men are included in this study. It is interesting to note that many of these men are included in the groups showing (*a*) signs of minimal disease; (*b*) indefinite signs, and (*c*) no signs of disease. In a considerable number of cases the roentgen ray revealed evidence of slight parenchymatous disease above the first rib on one or both sides, peribronchial tuberculosis, or no evidence of disease. In view of these facts, the ex-service men show a rather high average vital capacity percentage. In civil life patients often come late for diagnosis possibly because of the physician's fee, or many have dependents to support and do not give up work until forced to do so by moderately or far advanced disease. In the case of ex-service men the government provides for transportation, free examination, free observation and treatment, and compensation in cases of active disease traceable to service. Under these conditions very few men have a fear of a diagnosis of tuberculosis, and, in fact, a few desire it. This condition is making possible the diagnosis of many early cases of pulmonary tuberculosis. On the other hand, some cases of slight and insignificant lesions of long standing are being diagnosed and placed in hospitals for treatment and recommended for compensation.

We have seen that a considerable number of cases with signs of minimal and moderately advanced disease, many of whom are confirmed by stereoroentgenograms, show a vital capacity percentage within normal limits. This fact may be explained in one or all of the following three ways: (1) We know that some of these patients had over-

developed vital capacities, and although they are now reduced considerably they still have capacities which appear to be within normal limits. (2) A few of the patients have tuberculous lesions which are very definite, although at present they are clinically insignificant. The percentage of cases which fall into this class will be ascertained only through further observation over a considerably longer period of time. (3) There is some evidence to suggest that the normal standards now employed are not quite applicable for the people of all parts of the United States. Dreyer's work [3] was carried out in England and the normal standards derived from his formulas are mostly commonly used today. Dreyer suggests, however, that the normal standards be ascertained for the people of various countries. Heise [4] in reporting the vital capacity findings on sixty-five patients in the Trudeau Sanatorium remarked that the test was not of great value to him as many patients had vital capacities within normal limits. Many of my vital capacity percentages also have seemed too high. From the present evidence it would appear that the people of the United States, particularly of the Middle West, have a greater vital capacity than the people of England. I have already [5] undertaken to throw some light on this subject, not by the use of mathematical formulas alone, but by actual observations made on several thousand individuals in various occupations. Observations have already been made on several hundred persons and the accumulation, compilation and analysis of these data are proving to be a tremendous task, the completion of which will require a long period of time.

SUMMARY

1. Vital capacity readings were taken in 335 cases suspected of having pulmonary tuberculosis. Stereoscopic plates were made in 210 cases.

2. In thirty cases in which stereoroentgenograms showed no evidence of disease the mean vital capacity was 102 per cent. of the normal, while the range was between 82 and 122 per cent. of the normal.

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3. Dreyer, G.: Investigations on the Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227 (Aug. 9) 1919. Dreyer, G., and Burrell, L. S. T.: The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet **1**:1215 (June 5) 1920. Dreyer, G.: The Assessment of Physical Fitness by Correlation of Vital Capacity and Certain Measurements of the Body. Paul B. Hoeber, New York City, 1921.

4. Heise, F. H.: Tr. National Tuberculosis Association, 1921, p. 140.

5. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease. II. A Study of the Vital Capacity and Physical Fitness of Nurses, with Tables Showing Calculated Vital Capacities for Normal Men and Women and a Method for Quickly Obtaining an Expression of an Individual's Physical Fitness, Journal-Lancet **41**:252 (May 1) 1921. III. The Value of Vital Capacity Readings in Clinical Medicine, Minnesota Med. **4**:635 (Nov.) 1921.

3. The stereoroentgenograms showed peribronchial tuberculosis in thirty-nine cases. The average vital capacity of these cases was 97 per cent. and the range was from 81 to 121 per cent. of the normal.

4. There were seventy-one cases with unilateral and seventy cases with bilateral parenchymatous tuberculosis revealed by the stereoroentgenograms. These cases were grouped according to the extent of disease revealed. Among these groups the vital capacity percentages were usually found to decrease as the extent of the disease increased.

5. On the basis of the physical examination, sixty-two cases showed no evidence of pulmonary tuberculosis. Ten per cent. of these cases had a vital capacity between 80 and 90 per cent. of the normal while the remainder were all well within the normal limits.

6. There were twenty-eight cases in which physical signs caused the diagnosis to be reserved. Approximately 4 per cent. of these patients had vital capacities between 70 and 80 per cent. of the normal, and approximately 3 per cent. more had vital capacities between 80 and 90 per cent. of the normal. The remainder of these were within normal limits.

7. There were signs of minimal tuberculosis in seventy-two cases, moderately advanced tuberculosis in 100 cases, and far advanced tuberculosis in seventy-three cases. In the majority of cases the vital capacity was found to be decreased in proportion to the extent of involvement revealed by the physical signs.

8. Pulmonary cavities were revealed by the roentgen ray in thirty cases. The mean vital capacity for this group was found to be 64 per cent., while the range was between 31 and 109 per cent. of the normal.

9. Nine cases had spontaneous or artificial pneumothorax. The mean vital capacity of this group was 49 per cent. while the range was between 32 and 58 per cent. of the normal.

2. BRONCHIAL ASTHMA

Staehelin and Schütze,[6] Plesch,[7] Peabody and Wentworth,[8] and others, have reported vital capacity findings in patients suffering from asthma. In some cases the vital capacity was considerably decreased while in others it was normal.

In this study observations were made on twenty persons suffering from bronchial asthma. Readings were taken during and at various

6. Staehelin, R., and Schütze, A.: Spirographische Untersuchungen an Gesunden, Emphsematikern und Asthmatikern, Ztschr. f. klin. Med. **75**:15, 1912.

7. Plesch, J.: Die pathologische Physiologie des Lungenvolumens und seine Beziehung zum Kreislauf, Ztschr. f. Exper. Path. u. Therap. **13**:165, 1913.

8. Peabody, F. W.; Wentworth, J. A., and Barker, B. I.: Clinical Studies on Respiration, Arch. Int. Med. **20**:433, 443, 468 (Sept.) 1917. McClure, C. W., and Peabody, F. W.: J. A. M. A. **69**:1954 (Dec. 8) 1917.

intervals between acute attacks. During acute attacks the vital capacity was found to be tremendously reduced, in some cases being as low as from 18 to 20 per cent. of the normal. With the disappearance of the attack, however, the vital capacity quickly returned to normal limits unless there existed some complication or other cause for a reduction. Different methods of treatment were employed; for example, some patients were given vaccines, others were given expectorants and in still others dietetic treatment was ordered. In most cases the vital capacity remained normal as long as the chest was kept free from râles. There were four cases in which asthma had extended over a period of many years. In none of these cases did the vital capacity return to normal limits after the disappearance of the asthmatic attacks. In each case the physical and roentgen-ray examinations revealed definite evidence of emphysema which was apparently sufficient to account for the reduced capacity. Three patients were beyond the age of 50. None of these quite returned to normal after the subsidence of their acute attacks. Since vital capacity decreases after the age of 40 or 50, the slight permanent reduction in these three cases was explainable on the age basis. The remaining cases showed vital capacities well within normal limits soon after the acute attacks had subsided.

SUMMARY

1. Vital capacity readings were taken in twenty cases of bronchial asthma.

2. The vital capacity was greatly reduced during acute attacks. In some cases it was reduced to from 18 to 20 per cent. of the normal.

3. After acute attacks subsided the vital capacity returned to normal in all cases except four with emphysema and three beyond the age of 50.

3. PNEUMONIA

In five convalescent cases of pneumonia Peabody and Wentworth [8] found the vital capacity to be between 71 and 114 per cent. of the normal. In only one of these cases, however, was there evidence of pulmonary involvement when the readings were taken. The authors call attention to the fact that in the cases which were below normal one must take into consideration the general weakness persisting after an acute infection. They also call attention to the difficulty experienced in taking lung capacity readings in cases suffering from pleurisy.

In the present work an attempt was made to study the lung capacity throughout the course of the disease, and, finally, to make a correlation of the patient's temperature, pulse, respiration and vital capacity at different stages. Observations were made on twenty patients. The

measurements and readings were taken in the usual manner, and the vital capacity percentages were calculated as previously described.[5] In a few of the cases the crisis occurred about the time the patients were admitted to the hospital or before observations were begun. In these

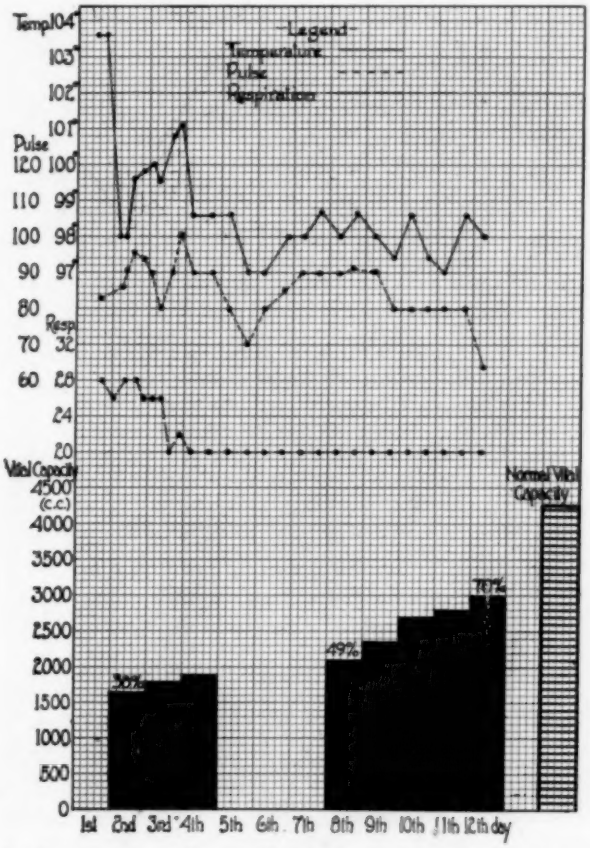

Fig. 2.—Temperature, pulse, respiration, and vital capacity curves in the case of a man, aged 58 (colored), suffering from lobar pneumonia involving the left lower lobe. Left hospital on the twelfth day with the vital capacity 70 per cent. of the normal.

cases, therefore, the study could be carried out only during convalescence. In a few other cases it was possible to begin the observations before any physical signs of pneumonia could be elicited. There was an occasional case omitted in which it was impossible to get accurate readings on account of severe pleurisy.

The curves (Figs. 2 to 7) show the temperature, pulse, and respiration for each day and the vital capacity readings on days when it was advisable to take such readings. In the last column of each chart is indicated the theoretical normal vital capacity for the given case. At

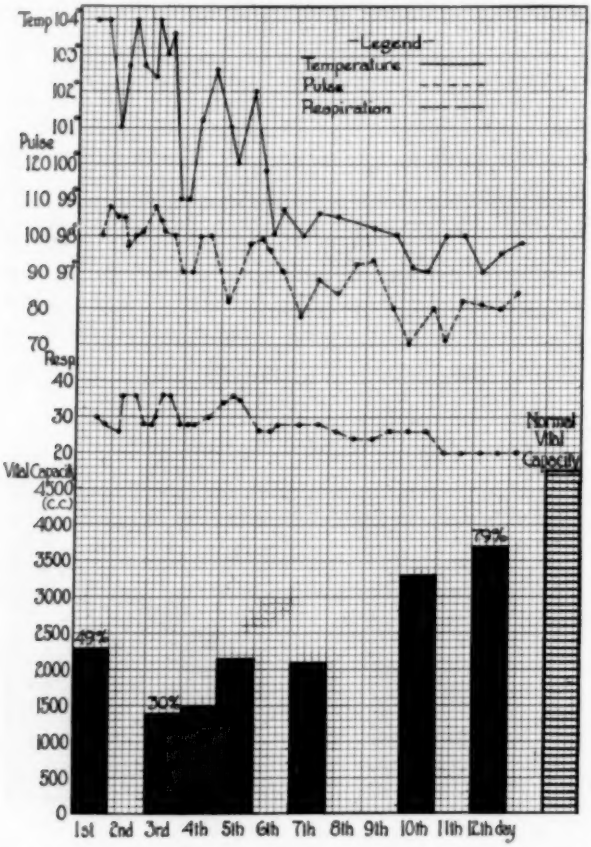

Fig. 3.—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 44, suffering from broncho-pneumonia with areas of involvement in both lower lobes. Left hospital on twelfth day with the vital capacity 79 per cent. of the normal.

the top of certain columns representing vital capacity is placed the vital capacity percentage of the patient for that day.

In observing the curves it is interesting to note that the vital capacity is very low from the beginning, in fact it is reduced to 50 per cent. or

less in most cases. This marked reduction of vital capacity from the beginning of a case of pneumonia is almost diagnostic. I have been able to go through good sized wards where the patients were suffering from acute disease (other than pneumonia) of the respiratory and

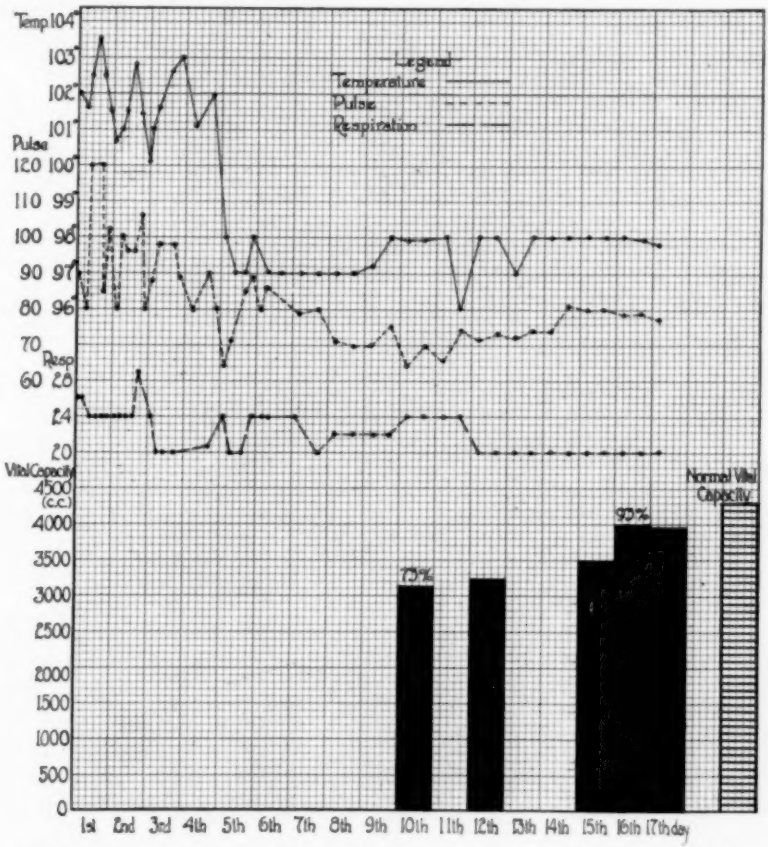

Fig. 4.—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 42, suffering from lobar pneumonia involving the right lower lobe. Left hospital on the seventeenth day with the vital capacity approximately 93 per cent. of the normal.

other organs, calculate vital capacity percentages of the patients and select all the cases on whom physical examination later proved developing pneumonia. It will also be observed from the curves that the lowest vital capacity is usually reached on or near the day of the crisis. From

this time on, if the patient recovers, the vital capacity gradually increases throughout convalescence. In one case of unresolved pneumonia, however (Fig. 7), the vital capacity remained almost stationary for a period of ten days following the crisis. In another case in which

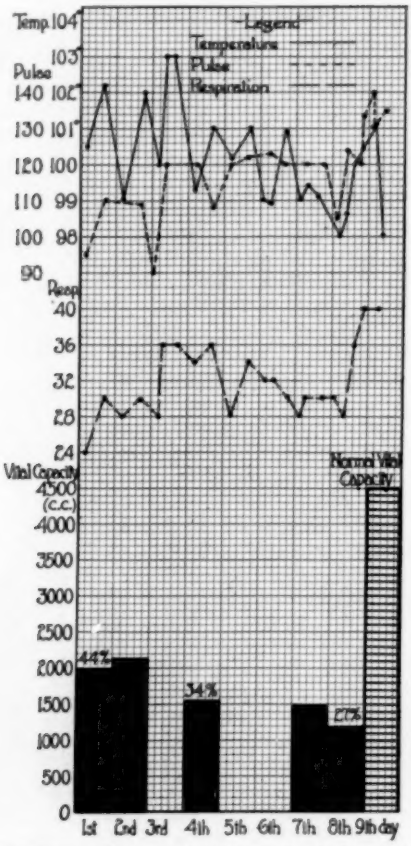

Fig. 5.—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 47, suffering from broncho-pneumonia with small areas of involvement in all lobes of both lungs. Exodus occurred on the ninth day. On the eighth day of the vital capacity was 27 per cent. of the normal.

tubercle bacilli appeared in the sputum during convalescence the vital capacity remained almost unchanged over a long period of time.

In the cases of pneumonia observed, the extent of involvement of lung tissue apparently made very little difference in the reduction of vital capacity, as cases in which physical and roentgen-ray examination

revealed disease limited to a single lobe or a part of one lobe showed a vital capacity as low as was present in cases with much more extensive involvement.

In minimal pulmonary tuberculosis, Garvin, Lundsgaard and Van

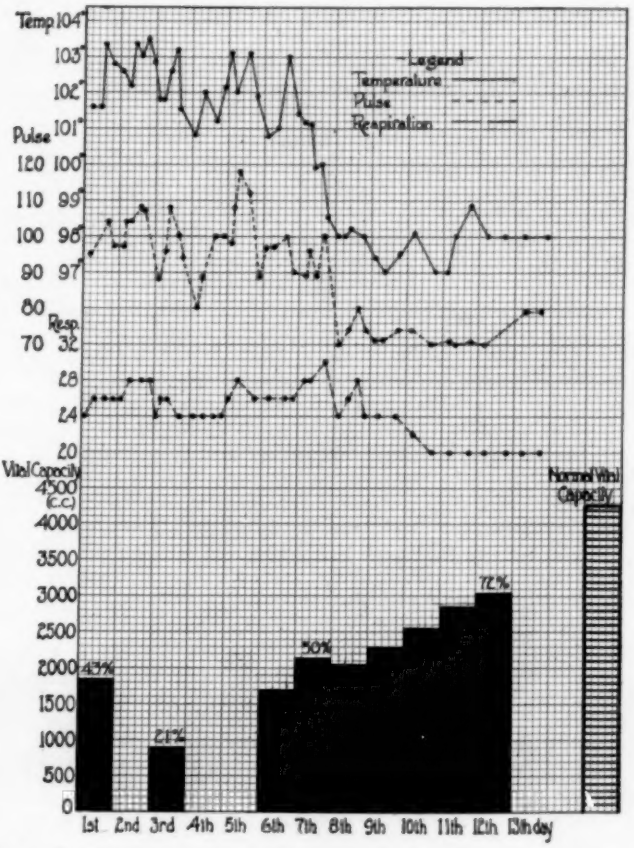

Fig. 6.—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 40, suffering from lobar pneumonia involving the left lower lobe. Left hospital on the twelfth day with the vital capacity approximately 72 per cent. of the normal.

Slyke[9] have shown that the reduction in vital capacity is due to increased residual air, while in the moderately advanced and far advanced stages the reduction is due to a decreased total capacity.

9. Garvin, A., Lundsgaard, C., and Van Slyke, D.: Studies of Lung Volume. II. Tuberculous Men, J. Exper. M. **27**:87 (Jan.) 1918. III. Tuberculous Women, J. Exper. M. **27**:129 (Jan.) 1918.

No attempt was made to ascertain the cause of the reduced vital capacity in pneumonia. Means and Barach [10] call attention to the fact that in pneumonia the extent of the pulmonary consolidation bears no constant relationship to the intensity of the dyspnea. As mentioned above, this is also true as regards vital capacity. Means and Barach

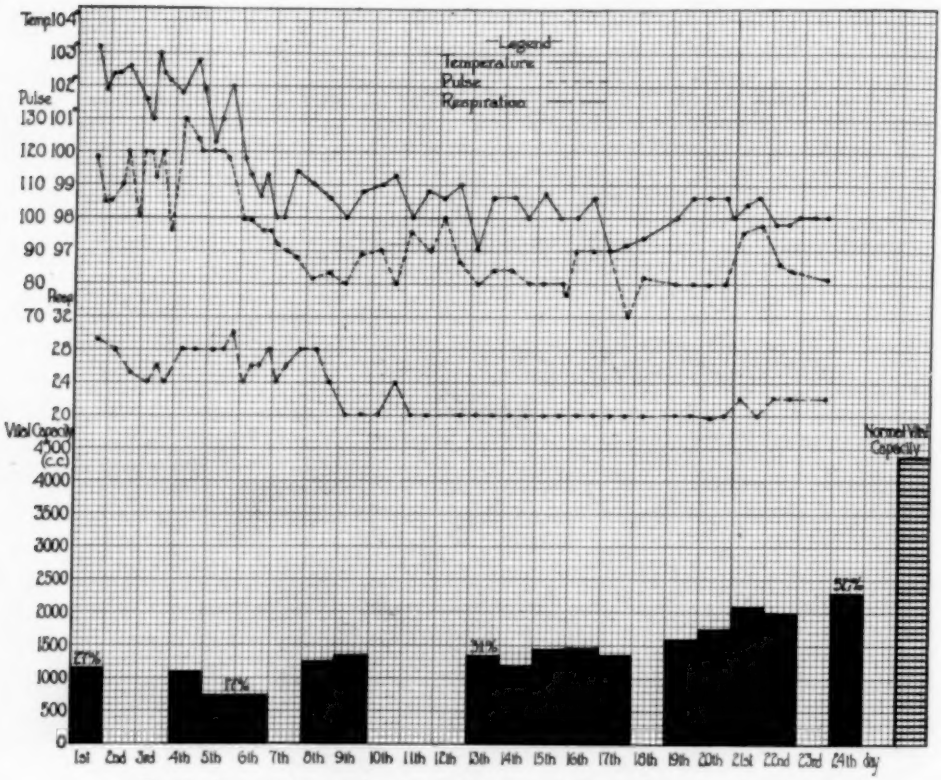

Fig. 7.—Temperature, pulse, respiration and vital capacity curves in the case of a man, aged 23, suffering from lobar pneumonia involving the entire right lung and the upper lobe of the left lung. The lowest vital capacity recorded was 17 per cent. of the normal which occurred on the fifth and sixth days. This is a case with delayed resolution. Patient left hospital on the twenty-fourth day with a vital capacity of 52 per cent. of the normal.

further point out that dyspnea may cease when the crisis is past with no alteration in the anatomic process in the lungs. This does not hold

10. Means, J. H., and Barach, A. L.: The Symptomatic Treatment of Pneumonia, J. A. M. A. **77**:1217 (Oct. 15) 1921.

true for vital capacity. Figures 2 to 7 show that the vital capacity is increased almost immediately after the crisis, but does not return to normal for many days.

SUMMARY

1. Observations were made on twenty patients suffering from pneumonia.

2. The lowest vital capacity taken was 17 per cent. of the normal. This occurred in one case on the fifth and sixth days of the disease. The highest reading taken was 93 per cent. of the normal. This occurred in another case on the day of discharge from the hospital.

3. There was very little relation between the extent of involvement of lung tissue and the reduction of vital capacity.

4. There is probably no other acute disease of the respiratory tract which so reduces the vital capacity from the beginning as pneumonia. Therefore, the vital capacity test is a valuable aid in early diagnosis.

5. During the period of convalescence the vital capacity test offers much information as regards the clearing up of the lesion. An unresolved condition or a complication is indicated by a failure of the vital capacity gradually to increase.

6. The vital capacity is of great value in guiding the patient's activities. Ordinarily patients are discharged from hospitals and allowed to become quite active before their vital capacities have reached a height consistent with such activity. Every patient should remain reasonably inactive in the hospital or the home until the vital capacity has reached at least 90 per cent. of the normal.

4. PARATYPHOID FEVER

Peabody and Wentworth [8] suggested that the reduced vital capacity which is present in patients convalescing from pneumonia may occur in any severe acute infection. Owing to the fact that my observations showed that reduction of vital capacity in pneumonia is not always consistent with the extent of involvement of lung tissue, it was again suggested by several physicians that the high fever and weakness resulting from the toxic condition were responsible for the greater part of the reduction in vital capacity.

Peabody and Sturgis [11] studied the effect of general weakness and fatigue on vital capacity. Most of their patients used in the general weakness series were suffering from pernicious anemia; however, one

11. Peabody, F. W., and Sturgis, C. C.: Clinical Studies of the Respiration. VIII. The Effect of General Weakness and Fatigue on the Vital Capacity of the Lungs, Arch. Int. Med. **28**:501 (Nov.) 1921.

patient had typhoid fever. In none of these cases without heart or lung disease was the vital capacity reduced more than 26 per cent. below the normal. In another series of cases an attempt was made to fatigue the muscles of respiration by taking the vital capacity every 15 seconds for 10 minutes. Contrary to what one might expect, the vital capacity was as great at the end of this experiment as at the

TABLE 3.—VITAL CAPACITY OF PARATYPHOID FEVER PATIENTS

	Hospital						Vital Capacity				
No.	Admitted	Discharged	Temperature Range	Pulse Range	Respiration Range	Duration of Fever	Date Taken	Temperature	Pulse	Respiration	Per Cent.
1	3/20/21	5/24/21	97–105	74–140	18–30	22 days	4/ 7/21	103	92	20	64
2	3/16/21	4/15/21	96–104	58– 98	18–22	21 days	3/22/21	103	84	22	65
							4/ 4/21	100	82	22	104
3	3/18/21	4/20/21	97–105	72–110	18–24	21 days	3/22/21	99	80	20	68
							4/ 7/21	101	88	20	94
4	3/25/21	4/14/21	97–103	60–122	16–25	14 days	4/ 6/21	102	98	22	71
5	3/19/21	4/18/21	97–104	68–124	18–26	16 days	3/22/21	102	100	22	72
							4/ 7/21	99	86	20	91
6	3/18/21	4/22/21	97–105	60–106	18–24	27 days	3/22/21	102	80	20	77
							4/ 7/21	99	64	20	75
7	3/23/21	3/28/21	96–102	64–100	18–22	3 days	3/25/21	100	80	18	78
8	3/22/21	4/12/21	97–102	54– 96	18–24	14 days	3/25/21	100	90	20	80
							4/ 4/21	99	80	20	107
9	3/21/21	4/21/21	97–104	64–108	18–26	20 days	3/22/21	104	92	24	80
							4/ 7/21	101	84	20	89
10	3/19/21	4/18/21	97–105	64–128	18–26	28 days	3/22/21	105	118	26	89
							4/ 4/21	102	106	22	96
11	3/29/21	4/12/21	96–104	60–110	16–24	9 days	4/ 4/21	101	96	20	90
12	3/27/21	4/12/21	97–102	60–108	18–22	10 days	4/ 4/21	99	72	18	90
13	3/23/21	4/20/21	97–104	64–100	18–26	18 days	3/25/21	100	96	22	91
							4/ 7/21	97	76	20	93
14	3/25/21	4/13/21	97–104	62–104	16–25	16 days	4/ 6/21	103	88	20	95
15	3/25/21	4/ 5/21	97–103	64–100	16–25	6 days	4/ 6/21	98	95	18	96
16	3/31/21	4/13/21	98–104	60–100	16–22	12 days	4/ 6/21	101	88	22	97
17	3/24/21	4/ 9/21	97–104	56–114	18–25	12 days	4/ 6/21	98	88	18	90
18	3/21/21	4/ 8/21	97–103	56– 92	16–24	16 days	4– 6/21	99	84	18	99
19	3/28/21	4/ 8/21	97–101	70– 96	16–22	8 days	4/ 6/21	98	84	20	100
20	3/22/21	4/11/21	97–104	60– 92	16–24	18 days	4/ 6/21	101	84	20	101
21	3/19/21	5/ 5/21	96–105	70–140	18–26	31 days	3/22/21	103	88	24	102
							4/ 7/21	99	96	20	106
22	4/ 1/21	4/ 7/21	97–100	82– 84	16–20	2 days	4/ 6/21	98	90	18	105
23	3/25/21	4/11/21	97–104	64–106	16–22	15 days	4/ 6/21	100	80	20	105
24	3/23/21	4/21/21	97/104	60–116	18–24	30 days	4/ 6/21	103	90	18	106
25	3/23/21	4/ 8/21	97–103	66–110	18–24	14 days	4/ 6/21	98	86	18	107
26	3/27/21	4/ 5/21	97–100	60– 94	18–20	2 days	4/ 4/21	98	94	20	108
27	3/27/21	4/12/21	97–101	60–112	18–22	15 days	4/ 4/21	99	84	20	110
28	3/25/21	4/17/21	97–104	72–116	18–25	20 days	4/ 6/21	101	98	20	110
29	4/ 1/21	4/ 5/21	98–100	82– 84	16–20	2 days	4/ 6/21	98	80	16	111
30	3/27/21	4/ 6/21	96–102	52– 86	16–22	5 days	4/ 4/21	98	84	20	117
31	4/ 1/21	4/17/21	97–103	60–102	16–24	17 days	4/ 6/21	102	88	20	117
32	3/26/21	4/ 9/21	98–102	64–114	16–25	13 days	4/ 6/21	99	80	18	131

beginning. The authors therefore conclude "that general muscular weakness and fatigue of the muscles of respiration are not important factors in causing the reduction of the vital capacity of the lungs in heart disease."

In March and April, 1921, an epidemic of paratyphoid fever occurred at the University of Minnesota which offered an excellent

opportunity to make a study of vital capacity in an acute disease outside the respiratory tract. About sixty cases were placed in the student hospital and it was through the kindness of Professor John Sundwall, director of the Student Health Service, that I was permitted to make observations on these cases. In all cases one reading, and in some cases two readings, were taken. The observations were made while the fever was present or soon after it had subsided. The vital capacity readings were taken with the patients in the reclining position, while the temperature was elevated, and in the sitting posture after the fever had subsided. In most of these cases the vital capacity readings taken at the time the students entered the University of Minnesota were on record in the Department of Physical Education. Inasmuch as some of the students had taken considerable athletic training since their admission to the university their vital capacities had been somewhat increased. In all cases the vital capacity percentage calculations were based on the theoretical vital capacity or the actual vital capacity observed at the time of admission to the university.

Table 3 shows the date of hospital admission and discharge, the temperature, pulse and respiratory range while in the hospital, the duration of fever and the percentage of vital capacity with the temperature, pulse and respiration of each patient at the time the vital capacity readings were taken. In this table the patients are arranged in the order of their vital capacity percentages, beginning with the lowest. Forty-one readings were taken on the thirty-two patients represented in this table. Of these forty-one readings only twelve showed a vital capacity below 90 per cent.; the remaining twenty-nine ranged from 90 to 131 per cent.

There were nine cases in which second readings were taken. Five of these showed a vital capacity below 90 per cent. on the first examination, but on the second examination the vital capacity had increased to 90 per cent. or more. In this series of nine cases there was only one case in which the vital capacity had not increased at the time the second observation was made.

The lowest vital capacity of the entire series was 64.3 per cent. It is interesting to note that before the vital capacity reading was taken this patient developed a rather severe pleurisy which apparently accounted, in part, for the low physical fitness percentage.

In Case 2 the vital capacity percentage was only 65.4 at the time of the first reading. About twenty-four hours later, the internist, with no knowledge of the results of the vital capacity test, recorded the presence of a slight cardiac disturbance believed to be due to toxemia. All signs of this disturbance disappeared in a few days and about two weeks from the time of the first reading the vital capacity was found to

be 104 per cent. It will be recalled that Peabody and Wentworth [8] and Nathanson and Ulrich [12] and others [13] have reported marked reduction in vital capacity due to true cardiac lesions.

At the outbreak of this epidemic all cases with similar symptoms were placed in the same wards. The vital capacity test was taken in most cases before a diagnosis was recorded. Three cases were found in which the vital capacity was reduced 50 per cent. or more. It is interesting to note that each of these patients was developing pneumonia, which later was revealed by physical examination.

In the remaining seven cases in which the vital capacity was reduced to below 90 per cent. of the normal, I have no explanation for the reduction unless it is due to toxemia. Unfortunately, however, these patients were not sent to the department of roentgenology nor were electrocardiographic studies made to find evidence of the presence or absence of deeply seated pulmonary lesions or the existence of heart lesions otherwise undiscovered.

Inasmuch as some of these cases at no time showed severe toxic manifestations, one hardly seems justified in trying to account for the reduction in lung capacity on the basis of toxemia.

It is interesting to note that in some of the remaining cases in which vital capacities were found to be within normal limits, the temperature ranged as high as 105 F., and the pulse ranged as high as 140 per minute.

SUMMARY

1. Observations were made on sixty patients suffering from paratyphoid fever.

2. Fifteen per cent. of these cases had vital capacities below normal limits. In more than 50 per cent. of these cases with reduced vital capacities, however, the reduction was explained on the basis of such complications as pleurisy or lung involvement.

3. In 85 per cent. of the cases the vital capacity was within normal limits.

4. In this study the vital capacity test was found to be valuable in suggesting beginning complications such as pleurisy and pneumonia.

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12. Nathanson, M. H., and Ulrich, H. L.: The Vital Capacity of the Lungs in Cardiac Disease, Minnesota Med. **4**:721 (Dec.) 1921.

13. Arnold, F.: Ueber die Atmungsgrösse des Menschen, Heidelberg, 1855. Hutchinson, John: On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Diseases by the Spirometer, Med. Chir. Tr. **29**:1846. West, H. F.: Clinical Studies on Respiration, VI. A Comparison of the Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306 (March) 1920. Wittich, F. W., Myers, J. A., and Jennings, F. L.: A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, J. A. M. A. **75**:1249 (Nov. 6) 1920.

The Hennepin County Tuberculosis Association made this work possible by establishing and supporting a research fellowship in tuberculosis in the University of Minnesota. Therefore, I wish to express my thanks to this association.

A part of this work was carried on in the Glen Lake Sanatorium and I am deeply indebted to Drs. E. S. Mariette, F. L. Jennings and H. A. Bendes for their valuable aid and cooperation. I desire to express my indebtedness also to Dr. W. J. Marcley, who made a part of this work possible in the Hopewell Sanatorium and the Thomas Hospital.

I wish to express my thanks to Professor R. E. Scammon for valuable suggestions and aid in plotting the Ogive curves here presented.

THE EFFECT OF THE ADMINISTRATION OF HYPERTONIC SALT SOLUTION ON THE BLOOD VOLUME AND CERTAIN RELATED BLOOD CONSTITUENTS*

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INTRODUCTION

Weed and McKibben [1] demonstrated that the intravenous administration of hypertonic salt solution to animals was attended by a decrease in the size of the brain and a fall in cerebrospinal pressure. These results were soon applied to patients by Cushing and Foley,[2] Sachs and Belcher [3] and others.[4] The usual intravenous dose was 100 c.c. 15 per cent. sodium chlorid solution (in some instances 30 per cent.). As a result of these injections cerebral herniae often disappeared or were much diminished, the swollen brain decreased in size so that operations on it could be performed more easily, and the elevated cerebrospinal pressure of patients with brain tumor was usually reduced promptly. The effects were, in general, so satisfactory that the adoption of intravenous hypertonic salt solution as a valuable therapeutic measure appeared likely. With these facts in mind, it seemed to us desirable to ascertain what alterations took place in the blood as a result of its use, and especially the degree and significance of these alterations. The various factors investigated were: the blood volume, blood chlorids, the relation between blood volume and blood chlorids, the effects produced on the red corpuscles and hemoglobin, and the oxygen and carbon dioxid content of venous blood. We regret that a greater series was not obtained for each factor, but this would

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* From the Medical Clinic of the Massachusetts General Hospital.

* This study is No. 28 of a series of studies on the physiology and pathology of the blood from the Harvard Medical School and allied hospital, a part of the expense of which has been defrayed by a grant from the Proctor Fund of the Harvard Medical School for the Study of Chronic Diseases.

1. Weed, L. H., and McKibben, P. S.: Am. J. Physiol. **48**:512, 1919.
2. Cushing, H., and Foley, F. B.: Proc. Soc. Exper. Biol. & Med. **17**:217, 1920.
3. Sachs, E., and Belcher, G. W.: J. A. M. A. **75**:667 (Sept. 4) 1920.
4. Cobb, S., and Ayer, J. B.: At the Massachusetts General Hospital. Personal communication.

have necessitated the withdrawal of an inconveniently large amount of blood. Since the procedure was relatively new and untried, it was undertaken only in the case of patients whose condition definitely indicated its use, a fact which further limited the series obtained. The intravenous human dosage was 100 c.c. of 15 per cent. sodium chlorid solution. The animals received a corresponding or relatively larger dose. Hypertonic salt solution was administered intravenously to seven patients, by mouth to one patient and one normal person and intravenously and by mouth to eight rabbits.

HISTORICAL

Blood hydremia has been observed in animals following the intravenous administration of hypertonic solutions by Brasol,[5] Kilkowitz,[6] Magnus [7] and others. Magnus demonstrated the hydremia following hypertonic salt solution by reduction in the hemoglobin percentage, the specific gravity and dried ash of the blood. No measurements of the absolute changes in plasma volume after hypertonic salt administration have been encountered. Other effects observed in animals have been a prompt diuresis, a depression of the freezing point of the serum,[7] a hyperglycemia and glycosuria,[8] and occasional fever.[9] Magnus [7] found that the increase in chlorids in the blood after the injection was apparently less than the chlorids introduced.

Hypertonic salt solution was first administered intravenously to patients by Velden [10] in 1909. Beginning with 5 c.c. of a 10 per cent. solution, he gradually increased the dose to 100 c. c. He discovered that a striking acceleration of the coagulation time of the blood took place, and used it with good results in cases of hemorrhage.[11] The diminished coagulation time after hypertonic sodium chlorid solution has been confirmed and has been shown to occur after the intravenous administration of other hypertonic salt solutions, as calcium chlorid [12] and sodium citrate.[13] It also occurs after the oral administration of sodium chlorid.[14] It has been supposed that some coagulation furthering substance present in tissue juice is drawn into the blood along with the

5. Brasol, L.: Arch. f. Anat. u. Physiol. S. 210, 1884.
6. Kilkowitz, S.: Arch. f. Anat. u. Physiol. S. 518, 1886.
7. Magnus, R.: Arch. f. Exper. Path. **44**:68, 1900.
8. Hirsch, E.: Ztschr. f. physiol. Chem. **94**:227, 1915.
9. Rolly, F., and Christjanson, A.: Arch. f. exper. Path. u. Pharmakol. **77**: 34, 1914.
10. Van der Velden, R.: Deutsch. med. Wchnschr. **35**:197, 1909.
11. Van der Velden, R.: Zentralbl. f. Herz. u. Gefässkrankh. **11**:61 (March) 1919.
12. Schenk, P.: Ztschr. f. d. ges. exper. Med. **11**:166, 1920.
13. Blumel: Med. Klin., 1910.
14. Neuhof, H., and Hirshfeld, S.: New York M. J. **133**:95 (Jan. 15) 1921.

tissue fluid. In man a hypoglycemia without glycosuria has been observed after the injection, in contrast to the hyperglycemia found in rabbits.[15]

It has recently been reported that the administration of hypertonic solutions produces a general inhibition of glandular secretions, including sputum, sweat, gastric juice, milk, bile and the thyroid secretion.[16] For these effects 50 per cent. dextrose solution was generally used in preference to hypertonic salt solution. The clinical results may be mentioned briefly. Night sweats have been diminished, gastric hyperacidity has been controlled, with relief of symptoms, and profuse expectoration associated with suppurative bronchitis, asthma, tuberculosis or pulmonary edema generally has been much decreased after the employment of these hypertonic solutions.[17] Profuse choleraic diarrhea and severe toxic dysenteries have been suppressed in like manner. In fourteen out of fifteen cases of hyperthyroidism and pronounced exophthalmic goiter, Stejskal[16] observed distinct diminution in the size of the thyroid after the injection of hypertonic solutions, with marked improvement in the symptoms and signs of the disease. Two of his patients continued to work two and three months, respectively, after treatment without evidence of symptoms. The glandular inhibition presumably arises because the tissue lavage into the blood diminishes the supply of fluid to the glands. It has been claimed also that there is an accelerated absorption of drugs introduced into the body, as sodium iodid by mouth, cocain applied to the mucous surfaces, and arsphenamin intravenously.[18]

Wynn[18] tried the effect of hypertonic salt in the treatment of neurosyphilis, since it has been shown that with the fall in cerebrospinal pressure a considerable amount of subarachnoid fluid entered the substance of the central nervous system.[19] He gave 200 c.c. of 15 per cent. sodium chlorid solution intravenously in the hour following intraspinal injection, but found no serologic or cytologic improvement over the usual course of intraspinal treatment. Corbus[20] and his co-workers used hypertonic salt as a method of spinal drainage, having shown that six hours after the injection there was a reabsorption of serum from the blood stream into the cerebrospinal fluid which carried the arsphenamin introduced intravenously into the spinal canal.

Bürger and Hageman[21] recommend .50 per cent. sugar solution (grape sugar) in doses of 1 gm. dextrose per kilo body weight. They

15. Schenk, P.: Ztschr. f. d. ges. exper. Med. **12**:269, 1921.
16. Stejskal, K.: Wien. klin. Wchnschr. **34**:200, 343, 1921.
17. Singer, G.: Wien. klin. Wchnschr. **34**:86, 1921.
18. Wynn, J.: Arch. Int. Med. **29**:72 (Jan.) 1922.
19. Foley, F. B., and Putnam, T. J.: Am. J. Physiol. **53**:464, 1920.
20. Corbus, B. C.; O'Conor, V. J.; Lincoln, M. C., and Gardner, S. M.: J. A. M. A. **79**:264 (July) 1922.
21. Bürger, M., and Hageman, E.: Deutsch. med. Wchnschr. **47**:207, 1921.

are now applying it to cases of lumbago and sciatica. In this country favorable results following hypertonic sugar solutions have been reported in influenzal pneumonia,[22] in other severe infectious diseases,[23] in traumatic shock,[24] and in glaucoma.[25] Such a varied usage of this relatively new therapeutic measure would seem to offer a wide field for future clinical research. In this report, in addition to the effect on the composition of the blood, the clinical results in the patients with increased cerebrospinal pressure will be mentioned.

METHODS

Absolute changes in blood volume were determined by the vital red method of Keith, Rowntree and Geraghty,[26] the principle of which depends on the color dilution of a known amount of dye when circulated in the blood stream. A sample of blood is first drawn, the dye is injected and allowed to circulate for three minutes for thorough mixing of dye and blood, and a second blood sample is withdrawn. The color dilution of the dye in the plasma gives a quantitative determination of the plasma volume, from which with the hematocrit, the total blood volume can be calculated. By utilizing the fact that no appreciable amount of the dye is excreted in the first ten minutes, it was possible to make a second determination of the blood volume within this period. The hypertonic salt solution was injected and a third blood sample was removed within this interval. Two readings were thus made on the identical quantity of dye injected, which served as an accurate control and in addition allowed the measurement of blood changes taking place immediately after the injection. Other methods of recording absolute blood changes are more time consuming and apt to result in a merging of the early swift changes in plasma volume. A third determination with this method is not possible for twenty-four hours, or until all traces of the dye have left the blood stream. Six satisfactory determination were made in this manner in Case 1 (Table 1).

Relative changes in blood volume were determined by changes in hemoglobin content, the red blood cell count, and the hematocrit percentage. The formula used was that of Boycott and Douglas,[27] and may be illustrated as follows:

$$\frac{120\% \text{ (hemoglobin before)}}{80\% \text{ (hemoglobin after)}} \times 100 = 150 \text{ per cent., or the blood}$$

22. Wells, C. W., and Blankinship, R. C.: J. A. M. A. **74**:75 (Jan. 10) 1920.
23. Litchfield, L.: J. A. M. A. **71**:503 (Aug. 17) 1918.
24. Erlanger, J.: J. A. M. A. **69**:1410 (Oct. 27) 1917.
25. Sansum, W. D.: J. A. M. A. **68**:1885 (June 23) 1917.
26. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: Arch. Int. Med. **16**:547 (Oct.) 1915.
27. Boycott, A. E., and Douglas, C. J.: J. Path. & Bacteriol. **13**:256, 1909; ibid. **16**:485, 1912.

volume after saline injection in per cent. of the normal or original blood volume.

This method depends on the assumption that the volume of circulating hemoglobin is constant under control conditions. It is known that the red corpuscle content of the blood is altered by a number of conditions, among them low oxygen tension,[28] fright,[29] exercise, sweating, administration of epinephrin, abdominal massage,[30] and also that it varies at different periods of the day.[31] Consequently, the calculation of the blood volume changes for any length of time on the basis of variations in red cell or hemoglobin percentages would seem to be fraught with error. Bogert, Underhill and Mendel,[32] however, found that the hemoglobin of rabbits did not vary appreciably for a period of several hours. In Case 1 of this series comparisons were made between the blood volume changes as determined by vital red method and the relative changes as determined by dilution of hemoglobin, red corpuscles and hematocrit. The immediate changes following the infusion were quite comparable, but at the end of twenty-four hours a discrepancy occurred. It seems probable that for short periods of time relative blood volume changes can be determined fairly by methods that depend on hemoglobin dilution, but for periods as long as twenty-four hours an error may be introduced.

The analyses of the blood oxygen and carbon dioxid were done by the method of Van Slyke and Stadie.[33] The hemoglobin was calculated from the oxygen capacity. The chlorid determinations were carried out by the method of Wetmore.[34] Except when the oxygen and carbon dioxid contents were determined, the blood was not withdrawn under oil. The influence of a diminishing tension of carbon dioxid on the distribution of chlorids between plasma and red corpuscles would make our figures for the plasma chlorids a little high.[35] For this reason no precise comparisons of the exchange of chlorids between plasma and cells following injection of hypertonic salt solution have been made.

In the case of rabbits the salt solution was injected into the ear vein, and the blood withdrawn from the heart. In the patients, the brachial veins were used.

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28. Fitzgerald: Quoted from Haldane, J. S.: Organism and Environment 1917, p. 52.
29. Lamson, J.: J. Pharmacol. & Exper. Therap. **7**:169, 1915.
30. Schneider, E. C., and Havens, L. C.: Am. J. Physiol. **36**:239, 1915.
31. Dreyer, G.; Bazett, H. C., and Pierce, H. F.: Lancet **1**:588, 1920.
32. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: Am. J. Physiol. **41**: 189, 1916.
33. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1, 1912.
34. Wetmore, A. S.: J. Biol. Chem. **45**:113, 1920.
35. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **30**:342, 1917. Fridericia, L. S.: J. Biol. Chem. **42**:245, 1920.

DISCUSSION OF RESULTS

Blood Volume.—The most striking result of the intravenous injection of hypertonic saline solution was an immediate and marked increase in the plasma volume. The administration of 100 c.c. of 15 per cent. sodium chlorid solution was followed within one or two minutes after the injection by an elevation of from 15 to 30 per cent. of the total blood volume, representing a pouring into the blood stream of from 500 to 1,200 c.c. of tissue fluid. The greatest increase in blood volume was noted approximately thirty seconds after the injection, i. e., as soon after as the blood could conveniently be drawn. From then on it progressively diminished, and in most cases returned nearly to the original volume within three and one-half hours. In one case in which the plasma volume was abnormally lowered before the injection, the increased blood volume persisted for four days. The factors that govern the magnitude, the time relationship, and the relative permanency of the changes in plasma volume may be grouped as follows: (1) the total increase in chlorids present in the entire circulating blood at the time of the analysis; (2) the condition of the kidneys. Other factors, such as the amount and concentration of the solution, the speed of injection, the weight of the subject, and the amount of chlorids in the body, may be considered subdivisions of the first group. In order to show how these factors explain the mechanism of the elevation in blood volume, the chlorid content of the entire blood was determined before and after the injection of hypertonic salt solution. The total increase in sodium chlorid was then compared to the increase in blood volume. It was found the volume response was essentially that which would fulfil the isotonic requirements of the increased salt. In other words, the normal isotonic concentration of the blood was in the main preserved. The detailed calculations follow.

The chlorid content of the entire circulating blood may be determined by multiplying the absolute blood volume by the chlorid concentration in grams per liter of whole blood. Similarly, the chlorid content of the entire plasma is determined by multiplying the plasma volume by the plasma chlorid concentration. The difference between these two figures gives the chlorid content of the entire red cells. With the hematocrit the chlorid concentration of red corpuscles in grams per liter can be calculated (Table 1). If, in case 1, these figures are charted graphically together with the blood and plasma volume after the intravenous administration of hypertonic salt solution, a close parallelism is found between the blood and plasma volume, on the one hand, and the total quantity of chlorid in the circulating blood or plasma on the other. Slight discrepancies exist which will be discussed later. Between the blood volume and the chlorid concentration in grams per liter of whole blood or plasma an approximate parallelism is present. In the other

TABLE 1.—Blood Alterations Following Intravenous Administration of Hypertonic Salt Solution. The Relation Between the Increase in Blood Volume and the Increase in Total Chlorids

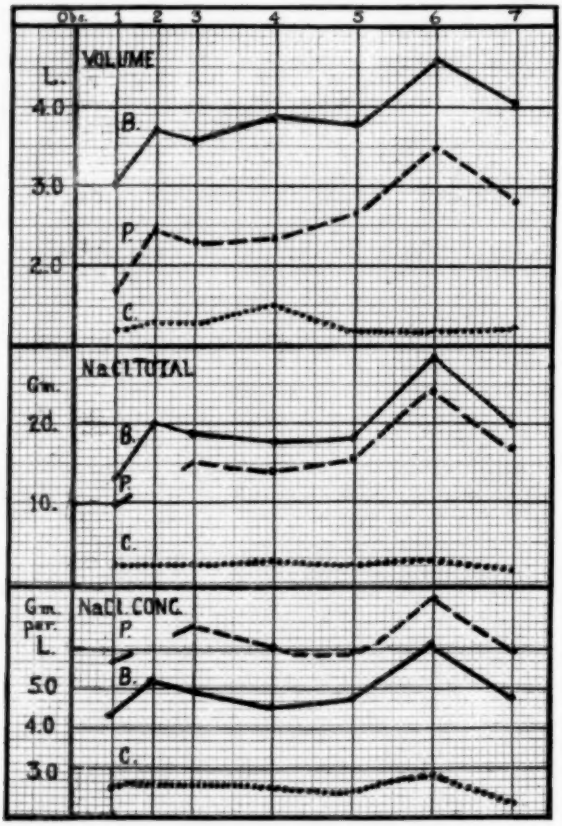
Case No., Age, and Diagnosis	Date	Time of Observation (Note: Each injection = 15 gm. NaCl in 100 c.c. of Water)	Hemoglobin (Calculated from Oxygen Capacity), per Cent.	Red Blood Cells, per C.Mm.	Hematocrit Cells, per Cent.	Blood Volume Data			Blood Chlorid Data							Comparison of Volume and Chlorid Data		Remarks
									Concentration in			Total in Circulating			Total Increase in Chlorids of Entire Blood, C Gm.	Actual Increase in Blood Volume	Volume Theoretically Necessary to Render Increased Chlorids Isotonic, C/0.9	
						Total Blood, C.c.	Total Plasma, C.c.	Total Cells, C.c.	Whole Blood, Gm. per Liter	Plasma A, Gm. per Liter	Cells B, Gm. per Liter	Blood, Gm.	Plasma, Gm.	Cells, Gm.				
1	5/26	Before 1st injection..	104.5	4,136,000	41.6	2,979	1,739	1,240	4.38	5.68	2.55	13.07	9.88	3.19	....	...	...	Stuporus and inarticulate; twitching of hands
26 years, Cyst of the cerebellum		2 min. after injection (duration of injection, 3 min.)	82.7	3,424,000	34.6	3,740	2,445	1,295	5.31	....	....	19.85	.....	....	6.78	761	754	
		1 hr. after injection..	88.3	3,480,000	36.0	3,618*	2,315	1,303	5.11	6.57	2.53	18.47	15.40	3.07	5.40	639	601	Brighter; slurring speech present
	5/27	24 hrs. after injection	90.6	3,480,000	39.0	3,880	2,363	1,517	4.60	6.01	2.41	17.85	14.20	3.65	4.78	901	532	
	5/31	Before 2d injection...	90.4	3,536,000	31.0	3,781	2,606	1,175	4.82	6.02	2.16	18.24	15.70	2.54	....	...	...	Twitching of hands continues
		½ min. after injection (duration of injection, 4 min.)	80.4	3,192,000	25.0	4,675	3,508	1,167	6.16	7.29	2.76	28.80	25.59	3.21	10.56	894	1173	
		3½ hours after injection	88.2	3,300,000	31.0	.....	.....	.....	5.35	6.68	2.38	.....	.....	....	....	...	...	Brighter; less twitching
	6/ 1	Before 3d injection... (24 hrs. after 2d injection)	86.2	3,328,000	30.8	4,075	2,819	1,256	4.85	6.17	1.88	19.77	17.38	2.39	1.53	294	170	Twitching again
		10 min. after injection (duration of injection, 7 min.)	72.7	2,840,000	25.0	.....	.....	.....	....	6.82	....	.....	.....	....	....	...	...	Unchanged
		3 hrs. after injection	83.3	3,392,000	30.6	.....	.....	.....	5.28	6.30	2.97	.....	.....	....	....	...	...	Brighter and stronger
	6/ 6	5 days after injection	91.7	.....	28.6	.....	.....	.....	4.54	5.46	2.27	.....	.....	....	....	...	...	Carpopedal spasm

* In this instance, the blood volume was calculated from the previous vital red determination and the relative difference in hematocrit. In all others the vital red method was used directely.

TABLE 2.—Blood Alterations Following Hypertonic Salt Solution

Case No., Age, and Diagnosis	Administration of Hypotonic Salt				Hemoglobin Calculated from Oxygen Capacity, per Cent.	Red Blood Cells		Hematocrit Red Cells, per Cent.	NaCl Concentration			Venous Blood			Blood Volume Calculated from		Fragility of Red Blood Cells	Remarks
	Amount	Duration	Avenue	Time of Observation		Capillary Blood, per C.Mm.	Venous Blood, per C.Mm.		Whole Blood, Gm. per Liter	Plasma A, Gm. per Liter	Red Cells B, Gm. per Liter	Oxygen Content, Vol. per Cent.	Oxygen Saturation, per Cent.	Carbon Dioxid Content, Vol. per Cent.	Hematocrit, per Cent.	Hemoglobin, per Cent.		
2 35 years Tumor of cerebellum	100 c.c. 15% NaCl	5 min.	Intravenous	Before.....	111.9	4,256,000	.....	35.3	4.72	6.31	1.81	15.83	76.5	51.0	100	100	Hemolysis 42-34; cells gone at 26	Marked stupor
				3 min. after..	87.1	3,480,000	.....	26.6	6.68	8.08	2.82	10.15	63.1	54.0	133	128	Hemolysis 38-32; cells gone at 24	
				24 hrs. after...	97.0	3,704,000	.....	34.5	6.17	7.13	4.35	15.84	88.5	48.0	102	115	Hemolysis 42-34; cells gone at 28	Wide awake; cheerful
3 40 years Tumor of cerebellum	100 c.c. 15% NaCl	8 min.	Intravenous	Before.....	116.3	.....	.....	41.4	4.74	5.77	2.56	9.03	42.0	60.3	100	100	Control cells plus plasma dilution; hemolysis 36-24	Stuporous
				12 min. after..	93.3	.....	.....	36.6	5.03	7.29	1.12	6.93	40.2	60.8	113	125	Control cells plus plasma dilution; hemolysis 36-24	More cognizant of surroundings
4 22 years Fracture of skull	100 c.c. 1500% Ringer's solution	5 min	Intravenous	Before.....	124.8	5,228,000	5,184,000	46.7	4.51	5.93	2.89	15.43	66.9	61.3	100	100	.....	Serum clear
				2 min. after..	120.5	5,160,000	4,728,000	42.0	4.83	6.33	2.76	14.43	65.3	57.0	111	104	.....	Serum hemolyzed
				20 hrs. after...	122.8	5,296,000	5,048,000	43.8	4.46	5.89	2.46	19.33	85.2	55.1	106	102	.....	Serum clear
5 26 years Normal	50 c.c. 15% NaCl	7 min.	By mouth	Before.....	115.2	4,928,000	.....	43.4	4.80	6.11	3.09	11.95	56.0	56.7	100	100	.....	One hour after lunch
				15 min. after..	115.7	4,824,000	.....	43.0	4.89	6.33	6.93	11.24	50.5	54.5	101	100		
				1½ hrs. after	108.7	4,712,000	.....	42.7	5.05	6.51	7.23	....	....	....	102	106		

human cases, as well as in the experiments on rabbits, an approximate parallelism between the relative blood volume after the administration of hypertonic salt solution and the chlorid concentration of whole blood or plasma is also present (Tables 1, 2 and 4). The chlorid concentration in the red corpuscles and the chlorid content of the entire red blood cells show no constant relationship to the blood volume.



Relation between blood volume and blood chlorids following the intravenous administration of hypertonic salt solution. Results obtained in Case 1: *B*, whole blood; *P*, plasma; *C*, cells. The upper group shows the total blood, plasma and cell volume, expressed in liters (L.); the middle group, the total sodium chlorid in whole blood, plasma and cells, expressed in grams; the lower group, the concentration of sodium chlorid in whole blood, plasma and cells, expressed in grams per liter.

Observation (Obs.) 1 was made just before an injection of 100 c.c. of 15 per cent. sodium chlorid. Obs. 2, two minutes after; Obs. 3, one hour after; Obs. 4, twenty-four hours after; Obs. 5, one hundred hours after and just before the second injection; Obs. 6, thirty seconds after the second injection; Obs. 7, twenty-four hours after the second injection.

It thus appears from the chart that the increase in total chlorids of either blood or plasma is proportional to the volume increase in either blood or plasma. It may be mentioned at this point that the increase in blood volume after hypertonic salt injection is due almost entirely to the increase in the plasma volume. An exception to this occurred in Case 1, twenty-four hours after the first injection, when apparently a considerable increase in cell volume took place. For the most part, however, the blood volume reflects the changes in the plasma volume. A more accurate basis for comparing the blood volume and the blood chlorids may be had by calculating the number of cubic centimeter of water theoretically necessary to bring the increased chlorids in the blood into an isotonic state. This is done simply by dividing the total chlorid increase in grams by 0.9. If this number, conveniently called the isotonic equivalent of the chlorid increase, is compared to the actual increase in blood volume reckoned in cubic centimeter, it is found that at times they are approximately equal to each other, and at other times there is a certain divergence (Table 1). When the actual increase in blood volume after injection of hypertonic salt solution is equal to the isotonic equivalent of the chlorid increase, it is evident that the blood remains isotonic. When the actual increase in volume is less than the number of cubic centimeter of water necessary to bring the increase in chlorids to isotonicity (less than the isotonic equivalent), the blood is obviously to some extent hypertonic, provided other conditions remain constant. Thus, in Case 1, after the first injection the increase in chlorid content of the entire blood was 6.78 gm., its isotonic equivalent was 754 c.c., and the recorded increase in blood volume 761 c.c. In this instance it would appear that the increase in blood volume was the amount necessary to bring the chlorid increase in the blood into an isotonic state, and consequently that the osmotic pressure of the blood remained approximately as it was before the injection, i. e., equal to a solution of sodium chlorid of a concentration of 0.9 per cent.

If the immediate changes after the second injection are now examined, the chlorid increase is seen to be 10.56 gm., its isotonic equivalent 1173 c.c., and the recorded increase in blood volume 894 c.c. In this case, 279 c.c. of fluid are theoretically still needed to bring the chlorid increase to an isotonic state. The blood would thus appear to be hypertonic, containing a total excess of 2.51 gm of chlorid above the physiologic concentration, or 0.537 gm. per liter.

The provision was made in these calculations concerning the isotonicity of the blood that the other factors involved remained constant. The other factors involved in maintaining the osmotic pressure of the blood do not, however, remain constant, but undergo marked changes. Their alterations complicate but at the same time strengthen the conclusions drawn.

Assuming that the osmotic pressure of the blood before the second injection was equal to that of physiologic solution of sodium chlorid, 0.9 per cent., the part played by the chlorids in the blood in maintaining the osmotic pressure is equivalent to 0.482 per cent. (The chlorid concentration of whole blood before the second injection was 4.82 gm. per liter.) There are, thus, 0.418 per cent. (of the osmotic pressure of the blood in terms of physiologic sodium chlorid solution) to be furnished by other substances, such as glucose, sodium bicarbonate, other salts, and colloids. After the second injection, the chlorid concentration of whole blood was 6.16 gm. per liter, an increase of 1.34 gm. per liter. It would appear at first glance that each liter of blood was hypertonic to the extent of 1.34 gm. per liter, whereas in the previous calculations from the increase in blood volume, the hypertonicity was estimated at 0.537 gm. per liter. The difference between the two, 0.803 gm. per liter, does not, however, represent additional hypertonicity, but takes the place of the osmotic substances other than chlorids that are lost from each liter of blood by dilution with tissue fluid. Thus, after the injection, 894 c.c. of new fluid was found in the blood stream. The substances making up the 0.418 per cent. of the osmotic pressure (glucose, sodium bicarbonate, etc.) of necessity spread equally throughout the new blood volume and become correspondingly diminished in each liter of blood, so that the concentration of these substances became 0.338 per cent., or a loss of 0.80 gm. per liter. This is equal to the discrepancy noted above, and represents a replacement by chlorid of the osmotic substances lost by dilution. The concentration of these substances after the injection, 0.338 per cent., plus the chlorid concentration after the injection, 0.616 per cent., equals 0.954 per cent., representing a hypertonicity equivalent to 0.54 gm. per liter, which corroborates the original calculation of 0.537 gm. per liter (0.338 per cent., or the concentration of the other osmotic substances in terms of sodium chlorid after salt injection, is derived as follows: 0.418 per cent. [concentration of substances before injection] $\times$ 3781 [blood volume before] $\div$ 4675 [blood volume after] $=$ 0.338 per cent.).

Similiar calculations applied to the results immediately after the first injection indicate that the blood was practically isotonic in this instance, corroborating the agreement between the isotonic equivalent of the chlorid increase and the actual increase in blood volume.

Twenty-four hours after the first injection, the actual increase in blood volume appears somewhat greater than the isotonic equivalent of the sodium chlorid increase. Thus, the sodium chlorid increase of the entire blood was 4.78 gm., its isotonic equivalent 532 c.c., the actual increase in blood volume 901 c.c. It must be remembered, however,

that the osmotic substances other than sodium chlorid which become diluted through the ingress of tissue fluid probably revert to their original concentration after twenty-four hours, and restore the osmotic substances lost by dilution. If this calculation is carried out on that basis, the blood concentration is practically isotonic. Similarly, the increase in blood volume twenty-four hours after the second injection is in excess of the isotonic equivalent, but that excess is again equivalent to the osmotic substances that presumably enter the blood from the tissues to maintain the original concentration. The calculation on this basis again yields a practically isotonic concentration. (Thus, 0.485 per cent. [concentration of osmotic substances before second injection] + 0.418 per cent. [chlorid concentration after injection] = 0.903 per cent.).

It would appear from these results that the total increase in chlorids present in the circulating blood at the time of analysis is the primary determinant of the blood volume following hypertonic salt solution injection. The amount of increase of the blood volume corresponds approximately to the amount of fluid necessary to render the increased chlorids isotonic.

The discrepancies, which occur twenty-four hours following the injection, have been explained above. Thirty seconds after the second injection, the blood was apparently to some degree hypertonic, inasmuch as the increase in blood volume did not fully meet the requirements for isotonicity. Thorough mixing of blood and chlorides was probably not established, so that this may not have represented the condition throughout the entire body. It will be remembered that a depression of the freezing point of the serum after hypertonic salt has been demonstrated in animals, but in these investigations the amount of salt injected was relatively much larger.

The second important factor in determining the permanency of the increased blood volume appears to be the condition of the kidneys. Boycott and Douglas [36] showed that after the injection in rabbits of a quantity of physiologic solution of sodium chlorid equal to the calculated blood volume, the original blood volume returned to normal within thirty minutes. Two thirds of the injected quantity left the circulation during the administration, the duration of which was five minutes. This occurs with both ureters ligated, but in rabbits in whom uranium nephritis had been produced, the blood volume failed to return to normal in the allotted time. When double strength Ringer's solution was injected, only one third of the injected amount left the circulation in the first five minutes. White and Erlanger [37] found that

36. Boycott, A. E., and Douglas, C. J.: J. Path. & Bacteriol. **19**:221, 1914.
37. White, H. L., and Erlanger, J.: Am. J. Physiol. **54**:1, 1920.

in dogs a strongly hypertonic solution of glucose and gum acacia solution caused a marked increase in relative blood volume which gradually fell but did not return to normal in several hours. Magnus [7] studied the diuresis taking place in rabbits after the intravenous administration of salt solutions of varying concentrations, and found the degree of diuresis ran parallel to the degree of blood dilution. Galeotti [38] found that the diuresis varied inversely as the molecular concentration of the blood. The urinary output could not be followed in the present study as most of the patients were incontinent. None of the patients had

TABLE 3.—Relative Blood Volume Following Hypertonic Salt Solution

Case No., Diagnosis, and Age	Administration of Salt Solution				Hematocrit Cells, %	Blood Volume Calculated from Hematocrit, %	Remarks
	Amount	Duration	Avenue	Time of Observation			
6 Brain tumor ? 30 years	100 c.c. 15% NaCl	5 min.	Intravenous	Before..... 1 min. after.... 2 min. after.... 30 min. after.... 1½ hrs. after... 24 hrs. after.....	47.2 36.9 36.8 39.3 39.0 41.2	100 128 128 120 121 114	Sleepy; severe headache Felt very hot Headache gone No longer sleepy Patient brighter; no headache
7 Brain tumor 28 years	100 c.c. 15% NaCl	7 min.	Intravenous	Before..... ½ min. after.... 1 min. after.... 3 min. after.... 3 hrs. after.....	46.0 39.1 42.5 44.0 44.0	100 118 108 105 105	Slight headache Face felt hot Headache gone
8 Brain tumor 29 years	100 c.c. 15% NaCl	12 min.	Intravenous	Before..... 1 min. after.... 3 min. after.... 10 min. after.... 22 min. after.... 40 min. after....	46.4 40.3 41.8 43.8 44.1 44.6	100 115 111 106 105 104	Headache Felt very hot Headache gone; no complaints
9 Polycythemia vera 55 years	100 c.c. 10% NaCl	3 min.	By stomach tube	Before..... 15 min. after.... 30 min. after.... 1 hr. after..... 1½ hrs. after...	72.0 69.0 68.4 67.5 67.8	100 104 105 107 106	

demonstrable nephritis. In some of the rabbits, however, chlorid retention was present in the blood, shown by the immediate increase in blood chlorids failing to drop to normal subsequently. In these rabbits there was a parallel maintenance of the increased blood volume. Instances of the normal reaction in rabbits, an abrupt rise in blood volume immediately after the injection followed by a gradual fall, may be seen in experiments 1 and 3 (Table 5). In experiments 5, 6, 7 and 8 (Table 4) the relative blood volume showed an immediate increase which either remained stationary or became further elevated, and the chloride concentration of the blood and plasma likewise remained elevated. It is to be remembered that the chlorids of the entire blood were

38. Galeotti, G.: Arch. f. Physiol., 1902, p. 200.

TABLE 4.—Blood Chlorids and Relative Blood Volume in Rabbits Following Hypertonic Salt Solution

Experiment Number and Weight of Rabbit	Administration of 15% Salt Solution				Hematocrit Red Cells, %	Red Blood Cells (Venous Blood), per C.Mm.	Blood Volume Calculated from		Blood Chlorid Concentration			Blood Withdrawn, C.c.
	Amount	Duration	Avenue	Time of Observation			Hematocrit, %	Red Blood Cells, %	Whole Blood, Gm. per Liter	Plasma, Gm. per Liter	Cells, Gm. per Liter	
4 2.4 kg.	3 c.c.	½ min.	Intravenous	Before	42.7	.....	100	...	4.68	6.01	2.98	17
				3 min. after	30.9	.....	141	...	6.15	7.25	3.72	18
				20 hrs. after	25.0	.....	...	...	4.76	5.71	1.92	17
5 3.2 kg.	7 c.c.	1 min.	Intravenous	Before	32.6	.....	100	...	4.76	5.79	2.62	7
				5 min. after	29.0	.....	112	...	5.52	6.68	2.69	7
				13 min. after	25.0	.....	130	...	5.39	6.49	2.12	7
				24 hrs. after	....	.....	...	...	5.52	6.59	....	7
6 2.2 kg.	5 c.c	1 min.	Intravenous	Before	46.0	.....	100	...	....	5.70	....	5
				2 min. after	34.6	.....	133	...	....	6.87	....	5
				12 min. after	36.4	.....	126	...	....	6.92	....	5
				1½ hrs. after	32.8	.....	140	...	....	6.56	....	5
				8 hrs. after	24.0							
				24 hrs. after	18.0							
7 2.8 kg.	18 c.c.	1 min.	By stomach tube	Before	36.6	.....	100	...	5.85	7.36	3.25	6
				10 min. after	30.9	.....	118	...	6.19	7.49	3.30	7
				1 hr. after	30.6	.....	119	...	7.01	8.35	3.98	6
				24 hrs. after	29.0	.....	126	...	7.25	8.42	5.10	6
8 2.5 kg.	18 c.c.	1 min.	By stomach tube	Before	19.6	2,720,000	100	100	5.64	6.51	2.09	7
				5 min. after	17.8	2,592,000	110	105	5.80	6.72	1.57	7
				30 min. after	18.4	2,096,000	106	130	6.30	7.30	2.12	6
				24 hrs. after	14.5	1,992,000	135	136	6.99	8.00	1.03	7

not obtained so that precise relationships between blood volume and blood salt are not intended. In experiments 7 and 8, the hypertonic salt solution was administered by stomach tube, the blood volume becoming progressively higher during the twenty-four hours following the ingestion of the salt, and the chlorid concentration of the blood steadily rising in parallel fashion. It becomes apparent from these data that in the case of rabbits unable to excrete salt the retention of chlorids in the blood is associated with the retention of an increased plasma volume.

There are other factors that have a more or less obvious bearing on the elevation in blood volume due to hypertonic salt solution. The slower the speed of administration, the less will be the amount of increase in blood volume, since the increased fluid is constantly leaving the blood stream. Where a uniform amount of solution is administered, the weight of the subject will be an evident factor. In Case 1, it was seen that 6.78 gm. of salt were found increased in the blood two minutes after the first injection of 15 gm., and 10.56 gm. one-half minute after the second injection of 15 gm. Granting that a certain amount of chlorids were excreted through the kidney and intestine, it is evident that the larger part was taken up by the tissues. Before the first injection the total chlorids, as well as the chlorid concentration were low, whereas before the second injection the total chlorids and the chlorid concentration were considerably higher. This suggests that the paucity of body chlorids in the first instance was responsible for the tissues taking up more chlorid than in the second instance, in which the chlorid concentration and total chlorids were already relatively high. The suggestion is purely a tentative one, and it must be admitted that the differing time intervals following the injection may be partly the cause of the discrepancy.

From our results in the series of patients studied, no typical curve of blood volume following the administration of hypertonic salt solution was found. It is obvious that there are sufficient reasons for this. The persons studied were not normal but severly ill. The treatment of each patient varied, and the diet and fluid intake likewise varied according to the therapeutic indications. Although a uniform amount of solution was generally given, this meant a varying dosage in terms of salt per kilogram of body weight. The speed of injection, as well as the time of making observations, was not kept constant. No typical response of the blood volume was thus found but certain general characteristics can be described as well as the probable mechanism.

After the intravenous injection a rapid rise in blood volume was followed by a gradual fall. The greatest increase appeared to be present immediately after, i. e., 30 seconds after the end of the injection. In all of the determinations, except one, a substantial return toward the original blood volume occurred in from one to three and

one-half hours after the injection (Tables 1, 2 and 3). In the one case referred to the elevated blood volume persisted for four days, an observation which was confirmed by a vital red determination. Estimations of blood volume from hemoglobin determinations twenty-four hours after the injection cannot be considered reliable, as pointed out earlier in this paper. It is believed, however, that relative variations in blood volume can fairly be told from hemoglobin determinations taken within from one to four hours of each other.

TABLE 5.—Relative Blood Volume Following Intravenous Administration of Hypertonic Salt Solution

Experiment Number and Weight of Animal	Injection of 15% NaCl			Hematocrit Red Cells, %	Blood Volume Calculated from Hematocrit, %	Blood Withdrawn, C.c.	Remarks
	Amount	Duration of Injection	Time of Observation				
1	8 c.c.	1 min.	Before.....	24.0	100	1	
3 kg.			7 min. after.....	13.5	178	1	Marked tachypnea
Rabbit			22 min. after.....	16.5	155	1	
			26 min. after.....	17.3	139	1	
			1½ hrs. after.....	18.5	130	1	No ill effects
2	3 c.c.	1 min.	Before.....	30.0	100	1	
3 kg.			½ min. after....	27.0	111	1	
Rabbit			5 min. after.....	27.0	111	1	
			30 min. after.....	27.5	109	1	
			45 min. after.....	27.0	111	1	
			2 hrs. after.....	27.0	111	1	
			3 hrs. after.....	21.5	139	1	
			24 hrs. after.....	21.2	...	1	No ill effects
3	7 c.c.	1 min.	Before.....	36.6	100	15	Ether anesthesia
3.5 kg.			3 min. after.....	23.9	153	15	
Cat			1 hr. after.....	30.0	122	15	

It is interesting to note that the example of a persistently elevated blood volume occurred in a patient who had an abnormally low plasma volume associated with a low blood chlorid concentration and a low total chlorid content. After the first injection, the plasma volume and the chlorid figures were approximately normal, and maintained their normality until the second injection. After the second injection, a rapid rise in blood volume occurred, followed by a substantial return to the previous figure in three and one-half hours, as shown by the hemoglobin determinations. Similarly, after the third injection, the relative blood volume (as calculated from the hemoglobin, red corpuscle, and hematocrit dilution) showed a sharp elevation, followed by a gradual fall, approaching normal in three hours (Table 1). The reason for this variation in response may, perhaps, be found in the tendency of the organism to revert to or maintain the normal. In the presence of a low blood volume and a low total chlorid content the increase in volume and chlorid content of the blood persisted. In the presence of a normal blood volume and blood chlorid the elevation above the normal on two occasions was quite temporary, returning largely to the normal

figures within three and one-half hours. It is freely admitted that this reasoning is hypothetical and may not at all account for the facts.

It was shown in Case 1 that the increase in blood volume was approximately equal to the number of cubic centimeters of water theoretically required to render the increased chlorids in the blood isotonic. On this basis, the maximum increase due to administration of 15 gm. salt would be 1,666 c.c. As a matter of fact, however, this amount is never actually reached since a certain portion of the chlorids enters the tissues or is excreted the moment it arrives in the blood stream. The maxium increase, expressed in terms of relative blood volume, varied in individual cases from 115 to 130 per cent. of the original blood volume. This would represent a range of increase of from 500 to 1,200 c.c. of tissue fluid. In the two instances in which the absolute blood volume was measured by the dye, the maxium increase was 761 c.c. after the first injection and 894 c.c. after the second injection.

In Case 4 (Table 2), 100 c.c. of 1,500 per cent. Ringer's solution (fifteen times stronger than standard Ringer's solution) was injected. This patient was unrelieved of his headache, and there was no fall in spinal pressure, as shown by manometer readings. It is interesting to note that the increase in blood volume and in blood chlorids was of very slight degree. The reason for this can, in part, at least, be accounted for by the lessened amount of chlorids present in Ringer's solution, but the changes still seem of lesser degree than one would expect. The serum directly following the injection was deeply hemolyzed, an effect presumably due to the excess potassium in the solution. It is of some interest to note that in this case a hypertonic salt solution was given without any fall in cerebrospinal pressure, and with minimal evidence of blood dilution. In the other cases so tested, the fall in cerebrospinal pressure was accompanied by considerable blood dilution. The findings strongly suggest that the drop in cerebral pressure when it does occur is due to a volume change dependent on egress of fluid from the brain to the blood stream.

In the two persons to whom the salt was administered by mouth either a smaller amount or a smaller concentration was given. The result was that a much smaller increase in blood volume occurred and that the maximum increase took place more than one-half hour after the injection rather than immediately afterward. The rabbits received a much larger dose by mouth than they did intravenously, but the resultant increase in blood volume was about the same in the two groups. The two rabbits, which received the salt by mouth showed a progressively increasing blood volume associated with a progressively increasing blood concentration, as was discussed above. It may be mentioned in this connection that Foley and Putnam [19] found that the

oral administration of hypertonic salt caused a fall in cerebrospinal pressure similar to the intravenous administration provided that larger amounts of salt were given.

Red Corpuscles and Hemoglobin.—There were no significant changes in the red blood cells, except their decrease in number due to dilution. No hemolysis occurred as a result of hypertonic sodium chlorid injection. In the case in which hypertonic Ringer solution was given, the hemolysis was probably due to the abnormal amount of potassium present. Examination of the serum spectroscopically for traces of hemoglobin or for increased amounts of bilirubin was done in two cases with negative results.[39]

In Case 2 (Table 4) the red cells showed a slight increased resistance to hypotonic saline three minutes after injection with a return to the normal fragility twenty-four hours later. Before the injection the chlorid content of the red corpuscles was 0.64 gm. per liter; three minutes after 0.75 gm. per liter; twenty-four hours after 1.50 gm. per liter. The finding of temporary lessened fragility is probably explainable on the supposition that the increased chlorid content of the cell had not been reduced to isotonicity within three minutes. In this case it appears that the red corpuscles had swollen at the end of twenty-four hours, inasmuch as the hemoglobin and red blood cell count still showed dilution and the hematocrit had largely returned to the original value. The striking increase in the chlorid content of the red cell from 0.64 to 1.50 makes this seem plausible. In Case 3 (Table 2) the fragility test was made with control cells but with equal quantities of the plasma before and after the injection of hypertonic salt solution. No change in fragility resulted from admixture with plasma taken after the salt injection.

Oxygen and Carbon Dioxid Content of Venous Blood.—The venous oxygen content was markedly lowered, reflecting and largely due to the diminution in oxygen capacity. There was in one instance (Case 2, Table 2) a lowering of the venous saturation that may have represented a slight slowing up of blood flow due to sudden increase in blood volume. In the other three cases, the lowering of the venous saturation was too slight to be significant. The carbon dioxid content of venous blood showed no constant or decided changes in the three cases in which this was carried out (Table 2).

Clinical Results.—No harmful effects following the administration of hypertonic salt solution were observed. The precaution was taken to exclude any case that gave evidence of renal disease. The six patients with brain tumor who had increased cerebrospinal pressure were all symptomatically improved. The symptoms that were especially relieved

39. These examinations were performed by Dr. Chester M. Jones.

were headache and stupor (remarks in Tables 1, 2 and 3). In one instance a patient was inarticulate before the injection and afterward could make herself understood by a slurring speech. The relief of symptoms generally lasted one day. One patient, who for six weeks had suffered continuously from severe headache and stupor, became wide awake and completely free from headache twenty minutes after the injection, and remained so for three days, when her symptoms began gradually to return. Among the immediate effects was the sensation of feeling very hot. All the patients who were able to talk complained of it. This disappeared within twenty or thirty minutes of the injection. There was a temporary rise in pulse rate of between five and fifteen beats and in systolic blood pressure of between 10 and 40 mm., maximal immediately after the injection and returning to normal usually within thirty minutes of the injection. In no instance was there a rise in temperature of more than 1 degree (F). In the patient, who had a fracture of the skull and to whom 1,500 per cent. Ringer's solution was given, no beneficial effects were observed. In the patient with polycythemia to whom the salt was administered by mouth, no definite change in condition was manifest.

SUMMARY AND CONCLUSIONS

1. Hypertonic salt solution was administered intravenously to six patients with brain tumor and to one patient with a fractured skull, by mouth to one patient with polycythemia and to one normal person, intravenously and by mouth to eight rabbits. Observations were made on the blood volume, the blood chlorid concentration, the total chlorid content of the blood, the effects on red corpuscles and hemoglobin, the venous oxygen and carbon dioxid content, and the clinical condition of the patients.

2. The immediate effect of the intravenous injection of 100 c.c. of 15 per cent. sodium chlorid solution was a marked increase in plasma volume. Reckoned in terms of relative blood volume, the increase was between 15 and 30 per cent. of the original blood volume, and the calculated increase on this basis between 500 and 1,200 c.c. of tissue fluid. In two instances in which the absolute blood volume was determined by the vital red dye method the maximum increase in one case was 761 c.c. and in the other 894 c.c. The increase in blood volume reflected and was almost wholly due to the increase in plasma volume.

After the injection there was a more gradual fall in blood volume, in most cases largely, although not entirely, returning to the original volume within three and one-half hours. In one case that had an abnormally low blood volume the increase persisted for four days.

3. An increase in blood volume followed the oral administration of hypertonic sodium chlorid, but was relatively of lesser degree and slower onset.

4. The mechanism of elevation and maintainance of the blood volume after hypertonic salt administration appeared to be dependent on the behavior of chlorids in the blood. Following the injection of 15 gm. sodium chlorid solution in two determinations in Case 1, there was found an increase of approximately 6 gm. in the first and 10 gm. in the second.

In the first instance the amount of increase in plasma volume was equal to the amount of water theoretically required to render the increased chlorids isotonic. In the second instance the plasma volume increase was slightly less than the theoretic requirement of the added chlorid, indicating that in a portion of the blood stream at least the blood was slightly hypertonic. Essentially, however, the increase in blood volume corresponded to the isotonic equivalent of the introduced salt. In the other human cases and in the animal experiments the rise and fall in blood volume generally ran approximately parallel to the blood chlorid concentration.

In rabbits showing an inability to excrete chlorid, the increased blood volume persisted elevated with a parallel maintenance of the increased blood chlorid concentration.

5. The red corpuscles showed no impairment due to the introduction of hypertonic sodium chlorid solution. In one case there was a temporary lessening of fragility. The oxygen carrying power of the hemoglobin was intact. There was no free hemoglobin spectroscopically, or any increase in bile pigment. In one patient, to whom a markedly hypertonic Ringer's solution was given, evidence of hemolysis appeared in the serum, due presumably to the abnormal amount of potassium present.

6. No significant changes in oxygen saturation or carbon dioxid content of the venous blood were found.

7. In the six patients with brain tumor, who had an increased cerebrospinal pressure, symptomatic improvement occurred in all. This was mainly manifested in the relief of headache and stupor. No harmful effects were observed. It appears likely that the fall in cerebrospinal pressure that follows the intravenous or oral administration of hypertonic salt solution is a volume change dependent on the egress of fluid from the brain to the blood stream.

We wish to express our thanks to Dr. Stanley Cobb and Dr. James B. Ayer for finding us neurologic cases at the Massachusetts General Hospital, and to Dr. James H. Means for his interest and aid during the course of the work.

BOOK REVIEW

ROENTGEN-RAY DOSAGE IN TREATMENT AND RADIOGRAPHY. By W. D. Witherbee and John Remer.

This book sets forth the authors' views on filtered and unfiltered dosage by roentgen rays, and gives a bird's-eye view of the field of usefulness for roentgen-ray therapy. Such information has been in great demand since the use of the rays has been so widespread. The quantities given for filtered roentgen-ray dosage assume the theory that at twice the skin-target distance the therapeutic effect is one-half as great. This is contrary to the statements of other writers and is contrary to the accepted laws for radiant energy which state that the quantity of rays varies inversely as the square of the distance. Readers who are accepting the quantities set down for filtered dosage should be aware of this departure from the usual computations and measurements.